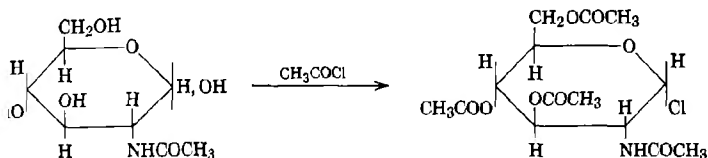


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**2-ACETAMIDO-3,4,6-TRI-O-ACETYL-2-DEOXY- α -D-
GLUCOPYRANOSYL CHLORIDE**

(Glucopyranosyl chloride, 2-acetamido-2-deoxy-,
triacetate, α -D-)



Submitted by DEREK HORTON¹

Checked by A. L. JOHNSON and B. C. MCKUSICK

1. Procedure

In a 500-ml. round-bottomed flask equipped with a magnetic stirrer bar and a reflux condenser protected by a tube of calcium chloride is placed 100 ml. of acetyl chloride; this operation and the subsequent reaction are conducted in a hood. The condenser is temporarily removed, and 50 g (0.226 mole) of dried 2-acetamido-2 deoxy-D-glucose (N-acetylglucosamine) (Note 1) is added in the course of 2 or 3 minutes with good stirring. The mixture is stirred for 16 hours without external heating at a room temperature of approximately 25°. The mixture boils spontaneously during the first hour of reaction. It is a clear, viscous, amber liquid at the end of the reaction (Note 2).

Through the condenser there is added 400 ml. of chloroform (u.s.p. grade), and the solution is poured with vigorous stirring onto 400 g. of ice and 100 ml. of water in a 3-l. beaker. The mixture is transferred to a 1-l. separatory funnel and shaken. The organic solution is drawn off without delay into a 3-l. beaker containing ice and 400 ml. of saturated sodium bicarbonate solution. The mixture in the beaker is stirred, and the neutralization is completed by shaking the mixture in the separatory funnel. The organic layer is run directly into a flask containing

about 25 g. of anhydrous magnesium sulfate. The entire washing procedure should be completed within 15 minutes (Note 3). The solution is shaken or stirred with the drying agent for 10 minutes (Note 4). The drying agent is separated on a 7.5 cm. Büchner funnel and is well washed with *dry, alcohol-free* chloroform or methylene chloride (Note 5). The filtrate passes through an adaptor directly into a 1-l. round-bottomed flask. The filtrate is concentrated to 75 ml. on a rotary evaporator at 50°, and dry ether (500 ml.) is rapidly added with swirling to the warm solution (Note 6). Crystallization usually begins after about 30 seconds. The flask is stoppered and set aside for 12 hours at room temperature.

The product is scraped from the walls of the flask and broken up by means of a curved spatula. The solid is collected on a 12.5-cm. Büchner funnel, washed with two 150-ml. portions of dry ether, dried by suction on the filter for 5 minutes, and stored in a desiccator over sodium hydroxide and phosphorus pentoxide. Analytically pure 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- α -D-glucopyranosyl chloride is obtained; weight 55–65 g. (67–79%); m.p. 127–128° (Fisher-Johns apparatus) (Note 7); typical $-\text{NHCOCH}_3$ absorptions at 6.09 μ and 6.49 μ in the infrared. Evaporation of the mother liquors and addition of ether to the concentrated solution gives an additional 4–6 g. (5–7%) of crystalline product, m.p. 125–127°, that is sufficiently pure for most purposes. The pure product may be stored in an open dish in a desiccator at room temperature for at least 3 years without decomposition (Note 8).

2. Notes

1. Suitable material is available from Pfanstiehl Laboratories, Waukegan, Illinois. It may also be prepared from the hydrochloride of 2-amino-2-deoxy-D-glucose (D-glucosamine) in 95% yield by the facile procedure of Inouye and co-workers.² The 2-acetamido-2-deoxy-D-glucose should be dried at 25° (1 mm.) for at least 12 hours before use. If this material is in the form of a powder rather than compact crystals, more acetyl chloride

may have to be added in order to get a stirrable mixture; the checkers found that an extra 50 ml. of acetyl chloride did not lower the yield.

2. The reaction mixture may be left for longer periods, as over a weekend, without adverse effect. If the ambient temperature is too low, undissolved material may be present after 16 hours, in which case a longer period of stirring is indicated, or the reaction mixture may be gently heated (not above 30°).

3. It is essential that isolation of the product be conducted rapidly and at 0° throughout, especially while the solution is acidic. All apparatus and solutions should be at hand before the reaction mixture is poured on ice. The product reacts fairly rapidly with water in the presence of an acid catalyst, undergoing acetyl migration to give the water-soluble 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy- α -D-glucopyranose hydrochloride.

4. An extended period of drying is unnecessary and should be avoided.

5. Commercial methylene chloride is usually sufficiently dry to use without pretreatment in place of dry, alcohol-free chloroform. The checkers used a pressure funnel under dry nitrogen for the filtration; filtration was rapid and exposure to atmospheric moisture was slight.

6. The solution must not be evaporated to a volume that permits crystallization to begin before the ether is added. The addition of ether should be sufficiently rapid that the heavy syrup is diluted to a clear, homogeneous solution before crystallization begins.

7. The checkers observed m.p. 118–119° when an open capillary tube containing a sample of analytical purity was placed in a stirred oil bath at 100° with the temperature rising several degrees a minute. The melting point of benzoic acid, determined simultaneously, was 122–123°. The checkers found $[\alpha]^{24D} + 110^\circ$ (c. 1.04, CHCl_3); literature values range from +109.7° to +118°.

8. Material of lesser purity may decompose within a much shorter time. If the product is exposed to moist air, it is converted into 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy- α -D-glucopyranose hydrochloride, which is insoluble in chloroform.

3. Methods of Preparation

The direct one-step preparation of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy- α -D-glucopyranosyl chloride was reported by Micheel and co-workers,³ and the described procedure is essentially the method of Horton and Wolfrom.⁴ The product was first prepared through a two-step route from 2-amino-2-deoxy-D-glucose hydrochloride by Baker and co-workers,⁵ and a number of adaptations of this method have been described⁶⁻⁸

4. Merits of the Preparation

The procedure permits acetylation of the sugar and replacement of the 1-acetoxy group by chlorine in one operation in only 2-3 hours of working time, gives good yields of pure product, and does not require gaseous hydrogen chloride. The two-step procedure from 2-amino-2-deoxy-D-glucose hydrochloride^{5,7} is time-consuming, and yields are very low if the acetylated intermediate is isolated.⁸ The yield is better when the second stage is performed without isolation of the intermediate,⁹ but gaseous hydrogen chloride is required, and the preparation takes considerably more working time than the method described.

The product is used in the preparation of glycoside, thioglycoside, and glycosylamine ("N-glycoside") derivatives of 2-acetamido-2-deoxy-D-glucose. A number of these compounds are of current interest, several seem to be involved in viral penetration of cells. The product has the α -D configuration and normally reacts to give glycosides with the β -D configuration, presumably through participation of the acetamido group in a bicyclic, closed-ion intermediate.

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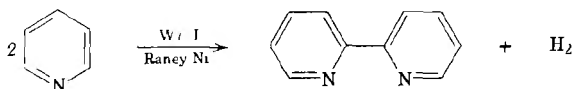
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2,2'-BIPYRIDINE



Submitted by W H F SASSE¹

Checked by VICTOR A SNIIECKUS and V BOEKELHEIDE

1. Procedure

A. *Degassed Raney nickel catalyst (W7-J). Caution! Raney nickel catalysts which have been prepared by the usual methods should not be heated in vacuum, as large quantities of heat and hydrogen may be given off suddenly, and dangerous explosions may result.*^{2 3}

In a hood a 2-l, wide-mouthed Erlenmeyer flask containing 600 ml of distilled water is placed in an empty water bath and fitted with an efficient stainless steel stirrer, so that its blades are half immersed. The stirrer is started, and 160 g of sodium hydroxide is dissolved in the water. Then 125 g. of 1:1 aluminum-nickel alloy (Note 1) is added in portions as rapidly as possible, but at such a rate that no material is lost by frothing with the stirrer running at full speed (Note 2). When all the alloy has been added the stirrer is slowed down, and the catalyst is washed down from the sides of the flask with distilled water. As soon as the reaction has subsided the water bath is filled with boiling water, and the catalyst is slowly stirred while the volume is kept up by the occasional addition of distilled water so that the catalyst is well covered at all times. After 6 hours, stirring and heating are discontinued, and the catalyst is allowed to stand at room temperature for 12-15 hours. It is then washed by decantation with ten 250-ml. portions of distilled water and transferred to a 1-l., round-bottomed, three-necked flask by means of dis-

tilled water. The total volume of catalyst and water is adjusted to 300 ml., and the flask placed in a cold water bath which is equipped with a thermometer. One side arm is fitted with a 100-ml. dropping funnel, and the other two necks are each connected to a 3-l. Büchner flask by short lengths of thick-walled, wide-bore rubber tubing (Notes 3, 4). One of the Büchner flasks is connected to a vacuum gauge and then to an efficient water pump. The other Büchner flask is connected directly to a second, equally efficient water pump. To control the pressure inside the apparatus, a screw clamp is placed between each Büchner flask and each pump (Note 5). With these clamps completely closed both pumps are turned on fully. The pressure inside the apparatus is now gradually reduced by opening the clamps at such a rate that no excessive frothing occurs. When both clamps are fully open, the water bath is heated slowly until the water in the reaction flask begins to boil. The bath is kept at this temperature until there is no more water left in the flask (Note 6). Then, with both clamps fully opened, the temperature of the water bath is raised to 100° during 15–20 minutes and kept at this temperature for 2 hours. After this time the catalyst is allowed to cool to 50–60°; it is now ready for use.

B. *2,2'-Bipyridine*. With the apparatus set as described above, 100 ml. of pure pyridine (Note 7) is poured into the dropping funnel, and the screw clamps are completely closed. Immediately afterward about 80 ml. of the pyridine is run slowly onto the catalyst from the dropping funnel. Under no circumstances is any air allowed to enter the flask. The flask is then shaken carefully in order to wet the catalyst as much as possible with pyridine. Another 80 ml. of pyridine is added in the same way, and the flask is shaken again. Finally 40 ml. of pyridine is added, and air is allowed to enter the flask. The connections to the Büchner flask are removed, and a reflux condenser is fitted. The reaction mixture is then boiled gently under reflux (Note 8). After about 48 hours the flask is allowed to cool to about 60°, and most of the liquid is decanted (*Hood!*) and filtered through a sintered-glass funnel (Note 9) into a 500-ml. round-bottomed flask. Then 50 ml. of fresh pyridine is added to the catalyst in the reaction flask, and the mixture is heated to reflux

for 10 minutes. The flask contents are allowed to cool to about 60° and the pyridine is decanted and filtered as before. This extraction is repeated two more times. The flask containing the filtrates is then equipped for vacuum distillation (Note 10), and most of the pyridine is removed on a water bath under reduced pressure (20–30 mm.) at a bath temperature not exceeding 40°. Toward the end of the distillation the bath temperature is raised to about 75° for 10 minutes (Note 11). The residue from this distillation is extracted with 100 ml. of boiling petroleum ether (Note 12), and the insoluble cream-colored material is collected by filtration and washed with three 25-ml. portions of the boiling petroleum ether (Note 13). The filtrate is chromatographed over alumina (Note 14) using petroleum ether (60–90°) for elution. The first 2 l. of eluate is collected, concentrated to 100 ml., and allowed to stand overnight in a refrigerator. The crude solid (23–24 g.) is collected and recrystallized from about 80 ml. of petroleum ether (60–90°) to give 21.0 g. of 2,2'-bipyridine as white crystals, m.p. 70–71° (Notes 15, 16).

2. Notes

1. The nickel-aluminum alloy used was supplied by British Drug Houses (through the Ealing Corporation in the U.S.A.). Average particle size was about 4 μ as measured by a Fisher Sub-sieve Sizer. Alloys of a finer particle size (about 2.85 μ) gave rise to considerable loss of catalyst during the washing and lost hydrogen during the degassing procedure in a much more vigorous fashion.

2. With a motor running at approximately 3500–4500 r.p.m. the addition of the alloy is completed in less than 10 minutes. Alcohol should not be added to the catalyst to control the frothing.

3. The Büchner flasks are included in the apparatus to accommodate relatively large quantities of hydrogen which are sometimes given off suddenly by the catalyst during the later stages of the degassing. Instead of Büchner flasks, strong round-bottomed flasks may be used.

4. Rubber tubing with diameters of 9 mm. I.D. and 17 mm. O.D. was used.

5. An air leak cannot be employed to regulate the vacuum inside the reaction flask since the catalyst becomes increasingly pyrophoric as the degassing progresses.

6. The average time required for the complete removal of the water from the catalyst varies from 4 to 12 hours. It is essential to evaporate the water slowly since much nickel may be lost if the water boils too vigorously. If the temperature of the bath should rise too high, the screw clamps are closed far enough to increase the pressure slightly in the apparatus. As soon as the bath has cooled to the required temperature, the clamps are reopened fully. The maximum practical temperature for the removal of the water was found to be 25–30° at pressures between 17 and 20 mm.

7. The pyridine used must be free of pyrrole since as little as 0.001% of pyrrole will markedly decrease the yield. The checkers found it most satisfactory to use spectroquality pyridine supplied by Matheson, Coleman and Bell. The submitters purified their pyridine by distillation from potassium hydroxide. To test for the presence of pyrrole, a 0.5-ml. sample of pyridine is diluted with 2.5 ml. of water, and 2 ml. of concentrated hydrochloric acid is added followed by 0.5 ml. of a 5% solution of *p*-dimethylaminobenzaldehyde in dilute hydrochloric acid (1:10 dilution of concentrated hydrochloric acid). If pyrrole is present, a red-purple color appears. Spectroquality pyridine gives a negative result in this test.

8. Excessive bumping will occur if the reaction mixture is heated too strongly.

9. A sintered-glass funnel (diameter 9 cm.) of medium porosity was used. The filtration is conveniently carried out under slightly reduced pressure, but care must be taken to keep any nickel on the funnel damp, as the catalyst is highly pyrophoric.

10. A relatively wide capillary (about 0.5 mm. I.D.) should be used to avoid blockages toward the end of the distillation.

11. The distillate contains, besides pyridine, small quantities of pyrrole, water, and 2,2'-bipyridine.

12. A petroleum fraction, b.p. 60–90° containing 5% of aromatics, was used throughout.

13. The petroleum-insoluble material is a nickel (II) complex containing 2,2'-bipyridine and 2,2'-pyrrolylpyridine.⁴ About 1.5 g. of this compound is obtained.

14. The checkers used No. 2 grade neutral alumina (Woelm) in a column 3.5 x 20 cm. If a more active alumina is used, larger quantities of petroleum ether are needed for the elution.

15. Small quantities of 2,2',2''-tripyridine are removed by this recrystallization.

16. Similarly 3- and 4-alkylpyridines give the corresponding 5,5'-dialkyl-2,2'-bipyridines and 4,4'-dialkyl-2,2'-bipyridines, respectively, in good yield when treated with W7-J nickel.⁵ Somewhat lower yields of 2,2'-biquinolines are obtained with quinolines.^{6,7}

3. Methods of Preparation

2,2'-Bipyridine has been prepared by the action of ferric chloride,^{8,9} iodine,¹⁰ or a nickel-alumina catalyst¹⁰ on pyridine at temperatures ranging from 300° to 400°. It has also been obtained from the reaction of 2-bromopyridine and copper.¹¹ The present procedure is a modification of a previously published, general method.³ The W7-J nickel catalyst was developed from the description of the W7 Raney nickel catalyst of Billica and Adkins.¹²

4. Merits of the Preparation

This procedure serves two purposes. It provides a synthesis for the important chelating reagent 2,2'-bipyridine, a substance of interest in several fields of chemistry, and it gives a preparation of an active, degassed Raney nickel catalyst.

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1-BROMO-2-FLUOROHEPTANE

(Heptane, 1-bromo-2-fluoro-)



Submitted by F. H. DEAN, J. H. AMIN, and F. L. M. PATTISON¹

Checked by P. B. SARGEANT and B. C. MCKUSICK

1. Procedure

Caution! Hydrogen fluoride is very hazardous. All operations must be carried out in a hood, and the precautions outlined in Note 1 should be followed.

A 1-l. polyethylene bottle is fitted with a three-holed rubber stopper. Three lengths of 0.25-in. (6-mm.) stiff polyethylene tubing extend through the stopper into the bottle. One length of tubing serves as an inlet tube for dry nitrogen, which is monitored by first bubbling through mineral oil. The second tube, the gas-outlet tube, carries a polyethylene drying tube packed with indicating Drierite[®]. These tubes extend only about 2 cm. into the bottle. The third tube serves as an inlet for anhydrous hydrogen fluoride and extends halfway into the bottle; it is connected to a hydrogen fluoride cylinder by a short length of Tygon[®] tubing secured to the cylinder outlet by copper wire. The bottle contains a Teflon[®]-covered magnetic stirring bar.

The bottle is flushed with dry nitrogen, and a slow stream of nitrogen passes through the bottle during all subsequent operations to ensure the exclusion of atmospheric moisture (Note 2). N-Bromoacetamide (80 g., 0.58 mole) is added (Note 3). The

bottle is cooled in a mixture of dry ice and acetone, and 250 ml. of anhydrous ether is added with efficient magnetic stirring. About 100 g. (100 ml., 5 moles) of anhydrous hydrogen fluoride is allowed to condense into the bottle with magnetic stirring (Note 4). This requires about 2 hours.

1-Heptene (49 g., 0.50 mole) (Note 3) is mixed with 50 ml. of anhydrous ether. The solution is added during 20 minutes through what was originally the nitrogen inlet; the hydrogen fluoride inlet now serves as the nitrogen inlet. The reaction mixture is stirred in the dry ice bath for an additional 4 hours. The dry ice bath is replaced by an ice bath, and the mixture is stirred for 40 minutes. It is then allowed to stand overnight in a mixture of dry ice and acetone in a Dewar flask.

A solution of 690 g. (5.0 moles) of potassium carbonate in 2 l. of distilled water is prepared in a 4-l. polyethylene beaker or pail, and 500 g. of crushed ice and 300 ml. of ether are added. The cold reaction mixture is cautiously added to the carbonate solution with stirring. The pH of the aqueous layer becomes about 9. The ether layer is separated, and the aqueous layer is extracted with three 200-ml. portions of ether. The ether solutions are combined and washed with three 100-ml. portions of water. The ether solution is dried over anhydrous sodium sulfate, and the ether is removed by distillation. The oily residue is fractionated through a 15-cm. Vigreux column under reduced pressure. There is a fore-run of about 0.5 ml., and then 59–75 g. (60–77%) of 1-bromo-2-fluoroheptane is collected at 70–78° (15 mm.); n_D^{25} 1.4408–1.4420. According to vapor phase chromatography, it is about 90% pure (Note 5).

2. Notes

1. Because of the hazardous nature of anhydrous hydrogen fluoride, *adequate precautions should be taken to protect the head, eyes, and skin.* Use of rubber gloves, an apron, and a plastic face mask is strongly recommended. All operations should be carried out in a hood. After completion of the reaction, all equipment should be washed with liberal quantities of water. A bottle containing magnesium oxide paste in glycerin should be available

in case of emergency. *Note! Burns caused by hydrogen fluoride may not be noticed for several hours, by which time serious tissue damage may have occurred.*

The checkers recommend that, if hydrogen fluoride comes in contact with the skin, the contacted area be thoroughly washed with water and then immersed in ice water while the patient is taken to a physician.

2. Moisture or inefficient stirring reduces the yield considerably.

3. Satisfactory sources of chemicals are: N-bromoacetamide, Arapahoe Chemicals, Boulder, Colorado; 1-heptene, Aldrich Chemical Co.; hydrogen fluoride, Matheson Co.

4. The amount of hydrogen fluoride is not critical. The amount of hydrogen fluoride may be estimated by condensing in enough to increase the volume of the reaction mixture by 100 ml.

5. According to vapor phase chromatography in a 6-ft. column at 150° over silicone grease, the product contains about 8% of one impurity and 2% of another. It is sufficiently pure for conversion to 2-fluoroheptanoic acid.²

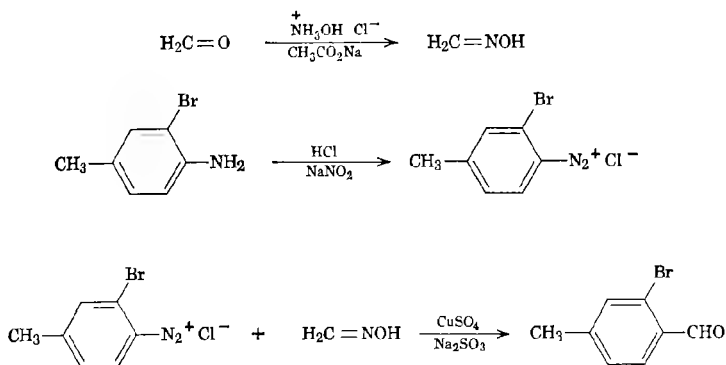
3. Methods of Preparation

1-Bromo-2-fluoroheptane³ has been prepared only by the present procedure, which is similar to one described by Bowers and co-workers.⁴

4. Merits of the Preparation

The method is general for forming *vic*-bromofluorides, which in turn are useful intermediates; this is exemplified in their conversion to 2-fluoroalkanoic acids.² The procedure can be applied, with minor modification, to many types of alkenes.³

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2-BROMO-4-METHYLBENZALDEHYDE**(*p*-Tolualdehyde, 2-bromo-)**Submitted by S. D. JOLAD and S. RAJAGOPAL ¹

Checked by A. G. SZABO and PETER YATES

1. Procedure

A. *Formaloxime*. A mixture of 11.5 g. (0.38 mole) of para-formaldehyde and 26.3 g. (0.38 mole) of hydroxylamine hydrochloride in 170 ml. of water is heated until a clear solution is obtained. Then there is added 51 g. (0.38 mole) of hydrated sodium acetate, and the mixture is boiled gently under reflux for 15 minutes to give a 10% solution of formaloxime.

B. *2-Bromo-4-methylbenzenediazonium chloride*. A mixture of 46.0 g. (0.25 mole) of 2-bromo-4-methylaniline ² and 50 ml. of water is placed in a 1-l. three-necked flask equipped with an efficient stirrer, a dropping funnel, and a thermometer. The stirrer is started, and 57 ml. of concentrated hydrochloric acid is added slowly. The mixture is cooled to room temperature, 100 g. of ice is added, and the temperature of the mixture is maintained at -5° to $+5^\circ$ by means of an ice-salt bath. To the stirred mixture there is added, dropwise, a solution of 17.5 g. (0.25 mole) of sodium nitrite in 25 ml. of water. After completion of the

addition, the stirring is continued for a period of 15 minutes. The stirred solution of the diazonium salt is made neutral to Congo red by the addition of a solution of hydrated sodium acetate (22 g.) in water (35 ml.) (Note 1).

C *2-Bromo-4-methylbenzaldehyde* A 3-l. three-necked flask is equipped with an efficient stirrer, a dropping funnel (Note 2), and a thermometer. The aqueous 10% formaldoxime prepared in step A is placed in the flask, and to it are added 6.5 g. (0.026 mole) of hydrated cupric sulfate, 1.0 g. (0.0079 mole) of sodium sulfite, and a solution of 160 g. of hydrated sodium acetate in 180 ml. of water. The solution is maintained at 10–15° by means of a cold-water bath and stirred vigorously. The neutral diazonium salt solution prepared in step B is slowly introduced below the surface of the formaldoxime solution (Notes 3 and 4). After the addition of the diazonium salt solution is complete, the stirring is continued for an additional hour and then the mixture is treated with 230 ml. of concentrated hydrochloric acid. The stirrer and the dropping funnel are replaced by stoppers, and the mixture is gently heated under reflux for 2 hours. The flask is set up for steam distillation, and the reaction product is steam-distilled. The distillate is saturated with sodium chloride, extracted with three 150-ml. portions of ether, and the ethereal extracts are washed successively with three 20-ml. portions of a saturated sodium chloride solution, three 20-ml. portions of an aqueous 10% sodium bicarbonate solution, and again with three 20-ml. portions of a saturated sodium chloride solution.

The ether is distilled and to the residue there is added, with cooling, 90 ml. of an aqueous 40% sodium metabisulfite solution, previously heated to 60°. The mixture is shaken for 1 hour and allowed to stand overnight. The solid addition product is filtered, washed twice with ether, and then suspended in 200 ml. of water in a 500-ml. flask, and 40 ml. of concentrated sulfuric acid is slowly added with cooling. The mixture is gently boiled under reflux for 2 hours, cooled, and extracted with three 100-ml. portions of ether. The ethereal extract is washed with three 15-ml. portions of a saturated sodium chloride solution and dried over anhydrous sodium sulfate. The ether is evaporated, and the product is distilled under reduced pressure. *2-Bromo-*

4-methylbenzaldehyde distills at 114–115° (5 mm.) as a colorless oil, yield 17.5–22.5 g (35–45%), which crystallizes in the receiver, m p 30–31°.

2. Notes

1 Exact neutralization of the diazonium salt solution is necessary in order to minimize coupling

2 The stem of the dropping funnel should extend a little below the surface of the solution in the three-necked flask.

3 Addition of the diazonium salt solution sometimes results in the formation of a pasty mass which prevents further stirring, the mixture is then allowed to stand for a further period of 1 hour

4 The checkers found it preferable to transfer the diazonium salt solution by siphoning under slight nitrogen pressure.

3. Methods of Preparation

The preparation of this aldehyde is based on the reaction due to Beech³ for the conversion of an aromatic amine to the corresponding aldehyde and has been described earlier by Jolad and Rajagopal⁴

4. Merits of the Preparation

This method of preparation of a halobenzaldehyde is of wide application and has been used for the preparation of the following substituted benzaldehydes: 2-bromo-5-methyl-,⁴ 2,3-dichloro- and 2,4-dichloro-,⁵ 2-chloro-4-methyl-,⁶ 2-methyl-4-bromo- and 3-methyl-4-bromo-,⁷ 2-methyl-5-chloro- and 2-methyl-5-bromo-,⁸ *p*-iodo-, *p*-fluoro-, 2-iodo-4-methyl-, and 6-iodo-3-methyl-.⁹

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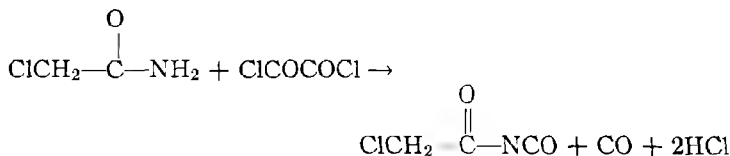
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α -CHLOROACETYL ISOCYANATE
(Isocyanic acid, anhydride with chloroacetic acid)



Submitted by A JOHN SPEZIALE and LOWELL R SMITH¹

Checked by LEIF A HOFFMANN and V BOEKELHEIDE

1. Procedure

In a 250-ml round-bottomed flask fitted with a magnetic stirrer (Note 1), a thermometer, and a condenser carrying a calcium chloride tube (Note 2) are placed 46.7 g (0.5 mole) of α -chloroacetamide (Note 3) and 100 ml of ethylene dichloride. The mixture is chilled in an ice bath to about 2° and stirred while 76.2 g (0.6 mole) of oxalyl chloride (Note 4) is added all at once. The mixture is removed from the ice bath, stirred for 1 hour, and then heated to reflux at 83° with stirring for 5 hours (Note 5). The solution is chilled in an ice bath to 0–10°, the condenser is replaced by a 120-mm distillation column packed with glass helices, and the solvent is removed at 70 mm pressure with stirring. The ice bath is removed after the solvent boils without foaming and is replaced by a heating mantle or oil bath. Distillation gives 39 g. (65%) of α -chloroacetyl isocyanate, b.p. 68–70° (70 mm.), as a colorless oil, n_D^{25} 1.4565.

2. Notes

1 For larger-scale preparations mechanical stirring is recommended.

2. Moisture must be rigorously excluded from the reaction mixture and the product.

3. The α -chloroacetamide was obtained from Eastman Kodak Co and used without purification.

4 The oxalyl chloride was obtained from Aldrich Chemical Co and used without purification. Oxalyl chloride vapor is irritating and toxic, and therefore manipulations must be carried out in a hood.

5 Because a large amount of hydrogen chloride is evolved, the reaction must be carried out in a hood.

3. Methods of Preparation

The only preparation reported for α -chloroacetyl isocyanate is that described by the submitters.²

4. Merits of the Preparation

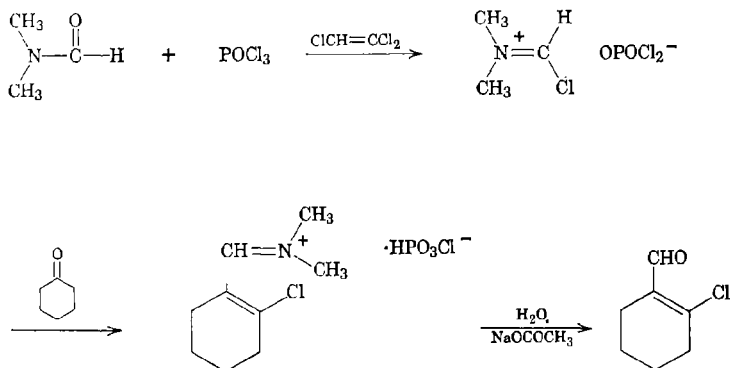
The procedure may be adapted for the preparation of other acyl isocyanates (*i.e.*, dichloroacetyl, trichloroacetyl, phenylacetyl, diphenylacetyl, benzoyl, etc) and is generally more convenient than the reaction of acid chlorides with silver cyanate^{3, 4} Acyl isocyanates react with amines, alcohols, and mercaptans to yield acyl ureas, carbamates, and thiocarbamates.

1 Research Department, Agricultural Division, Monsanto Company, St. Louis 66, Missouri

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3 O C Billeter, *Ber*, **36**, 3213 (1903)

4 A J Hill and W M Degnan, *J Am Chem Soc*, **62**, 1595 (1940)

2-CHLORO-1-FORMYL-1-CYCLOHEXENE**(2-Chloro-1-cyclohexenealdehyde)**Submitted by L. A. PAQUETTE,¹ B. A. JOHNSON,² and F. M. HINGA³

Checked by WILLIAM E. PARHAM and ROBERT W. GRADY

1. Procedure

To a 12-l. three-necked flask (Note 1) fitted with a stirrer, thermometer, reflux condenser, dropping funnel, nitrogen inlet, and calcium chloride drying tube are added 310 g. (4.24 moles) of dimethylformamide and 800 ml. of trichloroethylene (Note 2). The stirred solution is cooled to 5° with an external ice bath, and the system is blanketed with nitrogen (Note 3). Phosphorus oxychloride (460 g., 3.0 moles) is added during approximately 1 hour through the dropping funnel, the temperature of the stirred reaction mixture being maintained below 10°. The mixture is then allowed to warm to room temperature.

A solution of 320 g. (3.26 moles) of cyclohexanone in 800 ml. of trichloroethylene is prepared and is added to the stirred reaction mixture at such a rate that the temperature does not rise above 60° (Note 4). When the addition is completed, the mixture is heated at 55–60° for 3 hours.

The solution is cooled to below 35° by use of an ice bath, and

a solution of 1.2 kg. of anhydrous sodium acetate in 2.8 l. of water is cautiously added through the dropping funnel (Notes 5 and 6). The organic layer is separated and is washed twice with 1.5-l. portions of saturated aqueous salt solutions and once with 1.5 l. of deoxygenated water. The organic solution is dried over anhydrous sodium sulfate.

To the dried solution is added 10 g. of anhydrous sodium acetate. The solvent is evaporated under reduced pressure on a water bath heated to 50–60° (Note 7). The concentrate is distilled under nitrogen through a 14-in. vacuum-jacketed Vigreux column. The distillate is collected in receivers containing 1 g. of anhydrous sodium acetate per 100 ml. of flask capacity (Note 8). There is obtained 230–320 g. (53–74%) of colorless liquid, b.p. 86–88° (10 mm.), n^{20}_D 1.5198 (Notes 9 and 10).

2. Notes

1. The checkers carried out this procedure using a 5-l. flask and employed five-twelfths of the quantities of reagents specified.

2. Du Pont extraction grade of trichloroethylene was employed throughout the course of this work.

3. A nitrogen atmosphere is maintained over the reaction mixture and the product at all times when possible.

4. Approximately 1.5 hours is required to complete the addition.

5. The temperature is maintained below 35° during this addition, which is of approximately 1-hour duration.

6. The resulting two-phase mixture appears to be stable and may be allowed to stand overnight or for several days at room temperature.

7. The concentrate may be conveniently stored at –45° or below before distillation.

8. The aldehyde is quite unstable and tends to decompose with some violence on standing at room temperature. However, when treated with 1 g. of anhydrous sodium acetate per 100 ml. of distilled product, the compound has remained stable for 2 weeks when stored in this condition at room temperature. It may be stored quite indefinitely in this condition at –45°.

9. Gas chromatography is a convenient method of monitoring the distillation. Early fractions contain trichloroethylene and an unidentified reaction by-product

10 The product obtained by the checkers was pale yellow in color. The color was not removed by redistillation

3. Methods of Preparation

2-Chloro-1-formyl-1-cyclohexene has been prepared only by the action of phosphorus oxychloride (or phosgene) and dimethylformamide on cyclohexanone³⁻⁵ 2-Bromo-1-formyl-1-cyclohexene has been synthesized by a method analogous to the above by the use of phosphorus oxybromide or phosphorus tribromide.⁶

4. Merits of the Preparation

The described procedure is useful for the conversion of ketones to chloroalkene aldehydes Methyl ethyl ketone,^{3, 4} phenyl ethyl ketone, ^{3, 4} cyclobutanone,⁷ cyclopentanone, ³⁻⁵ cyclooctanone,³⁻⁵ α -tetralone,⁵ and benzosuberone⁵ are illustrative of the wide variety of ketones which have been so treated The yields are reported generally to be 65-80%.

The chlorovinyl aldehydes, although still a relatively new class of compounds, show great promise as useful synthetic intermediates^{3, 7, 8}

1 Department of Chemistry, The Ohio State University, Columbus, Ohio

2 Research Laboratories of The Upjohn Co, Kalamazoo, Michigan

3 Z Arnold and J Zemlicka, *Proc Chem Soc*, 227 (1958)

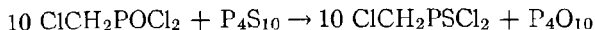
4 Z Arnold and J Zemlicka, *Coll Czech Chem Commun*, **24**, 2385 (1959)

5 W Ziegenbein and W Lang, *Ber*, **93**, 2743 (1960)

6 Z Arnold and A Holy, *Coll Czech. Chem Commun*, **26**, 3059 (1961)

7 J Zemlicka and Z Arnold, *Coll Czech Chem Commun*, **26**, 2852 (1961)

8 W Ziegenbein and W Franke, *Angew Chem*, **71**, 628 (1959)

CHLOROMETHYLPHOSPHONOTHIOIC DICHLORIDESubmitted by R. SCHMUTZLER¹

Checked by M. D. HURWITZ and W. D. EMMONS

1. Procedure

A 500-ml three-necked flask is provided with a mechanical stirrer, thermometer, and reflux condenser equipped with a drying tube. The flask is flushed with dry nitrogen and charged under nitrogen with 502 g. (3 moles) of chloromethylphosphonic dichloride (Note 1) and 160 g. (0.36 mole) of tetraphosphorus decasulfide (Note 2). The reaction mixture is heated under reflux with stirring for 6 hours, the liquid temperature being 180–190° (Note 3). The nearly black reaction mixture is then allowed to cool to room temperature and is distilled under reduced pressure. Material distilling between 70° (40 mm) and 150° (20 mm) is collected (Note 4). The yield is 364–396 g. (66–72%). There is no impurity in the material thus obtained which is detectable by gas chromatography (Note 5). The product may be redistilled if desired, although in most cases this is superfluous, b.p. 64–65° (10 mm); n_D^{25} 1.5730–1.5741 (Note 6). The P^{31} n.m.r. spectrum of the product shows a peak at -74.2 ppm relative to external phosphoric acid.

2. Notes

1. Chloromethylphosphonic dichloride is used as obtained from Stauffer Chemical Co. Alternatively it may be prepared from the reaction of phosphorus trichloride with paraformaldehyde.²

2. Technical tetraphosphorus decasulfide (Stauffer Chemical Co.) is employed. The product is weighed under nitrogen protection.

3. In order to prevent contact of the boiling reaction mixture with air, nitrogen is passed through a T-tube on top of the drying tube on the reflux condenser.

4. Toward the end of the distillation a thick residue is formed, and this makes the distillation difficult. After the contents of the distillation flask are cooled to room temperature, this residue may be disposed of by careful continuous rinsing with water under a well-ventilated hood

5. An F&M 500 Program-Temperature Unit (8 ft., 20% silicon rubber on 60-80 Super Support) was used for the VPC work: program 11°/min, flow 55 ml./min. Chloromethylphosphonothioic dichloride and chloromethylphosphonic dichloride, a potential impurity, are separated cleanly under these conditions.

6. Literature ³ values are: b.p. 89° (30 mm), n_{D}^{25} 1.5741, d_{25}^{25} 1.5891.

3. Methods of Preparation

Chloromethylphosphonothioic dichloride has been prepared by the reaction of chloromethylphosphonic dichloride with tetraphosphorus decasulfide ³⁻⁵ or with thiophosphoryl chloride under autogenous pressure ^{3, 5}

4. Merits of the Preparation

The reaction of chloromethylphosphonic dichloride with tetraphosphorus decasulfide ³⁻⁵ or with thiophosphoryl chloride ³ are the only methods of preparation for this compound reported. The method is applicable more generally, and the syntheses of methyl-, trichloromethyl-, ethyl-, propyl-, cyclohexyl-, phenyl-, and *p*-chlorophenylphosphonothioic dichloride from the corresponding phosphonic dichlorides have been reported ^{4, 5} Phosphinic chlorides of varying structures could also be converted to the corresponding thiono compounds by comparable procedures. ^{4, 6} The present method is preferable to the thiophosphoryl chloride procedure ^{3, 5} in that it does not require working under pressure.

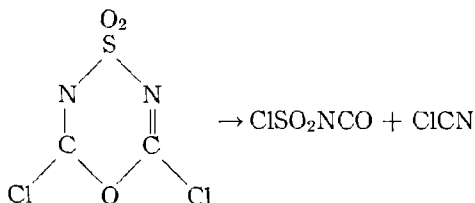
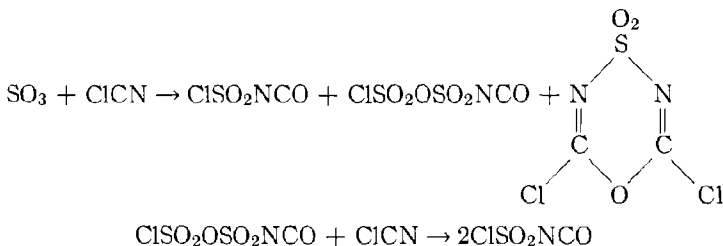
Chloromethylphosphonothioic dichloride is a reactive and

useful intermediate in organophosphorus chemistry.^{3, 4, 6} Of special interest is its desulfurization by trivalent phosphorus compounds such as phenylphosphonous dichloride leading to the formation of chloromethylphosphonous dichloride.³

- 1 Explosives Department, E I duPont deNemours and Company, Wilmington, Delaware
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- 3 E Uhing K Rattenbury, and A D F Toy, *J Am Chem Soc*, **83**, 2299 (1961)
- 4 M I Kabachnik and N N Godovikov, *Dokl Akad Nauk SSSR*, **110**, 217 (1956)
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CHLOROSULFONYL ISOCYANATE

(Isocyanic acid, anhydride with chlorosulfonic acid)



Submitted by RODERICH GRAF¹

Checked by JEROME F LEVY and WILLIAM D EMMONS

1. Procedure

Caution! Cyanogen chloride is extremely toxic. Sulfur trioxide and chlorosulfonyl isocyanate are highly corrosive materials. This

preparation should be carried out in an efficient hood, and rubber gloves should be worn throughout.

A 200-ml. four-necked flask is fitted with a mechanical stirrer (Note 1), a thermometer, a Claisen-type adapter bearing a dry ice reflux condenser and a dropping funnel, and a gas-inlet tube consisting of a length of 6-mm. glass tubing extending almost to the bottom of the flask. This gas-inlet tube is connected through a stopcock to a safety trap and then to a cylinder of cyanogen chloride (Note 2). The dropping funnel, protected with a calcium chloride drying tube, is charged with 64 g. (0.80 mole) of liquid sulfur trioxide (Note 3). The outlet from the dry ice condenser is connected to a trap cooled in dry ice.

The flask is charged with approximately 36.9 g. (0.60 mole) of cyanogen chloride while being cooled in a dry ice-methylene chloride slush bath (Note 4). The flask is allowed to warm to -5° to melt the cyanogen chloride, and then the liquid sulfur trioxide is added over a period of 0.75–1.25 hours. The reaction is very exothermic. During the addition the temperature is gradually decreased from -5° to -15° (Note 5). After addition is completed, the reaction mixture is checked for unreacted sulfur trioxide by adding approximately 1–2 g. of cyanogen chloride and noting if a temperature rise takes place. If necessary, this test is repeated until no more unreacted sulfur trioxide is left. The reaction mixture at this point is a pulpy, stirrable mass containing some chlorosulfonyl isocyanate, some chloropyrosulfonyl isocyanate, and much precipitated 2,6-dichloro-1,4,3,5-oxathiadiazine-4, 4-dioxide (Note 6).

The adapter bearing the dry ice condenser and dropping funnel is removed and replaced by a 16 cm. x 2 cm. distillation column packed with glass helices (Note 7) and connected to an efficient air-cooled condenser. The condenser has a 100-ml. receiver and is connected to a trap cooled in dry ice and protected by a drying tube to condense unreacted cyanogen chloride. The reaction flask is heated for about 1 hour while the temperature is gradually increased to 110 – 115° . At this point, cyanogen chloride is bubbled into the reaction mixture at the rate of about 0.010 mole/min. (Note 8). The temperature of the flask is raised to 120 – 130° , whereupon chlorosulfonyl isocyanate begins to distil

at a head temperature of 90–105°. When the distillation rate begins to slacken, and after most of the contents of the flask has distilled, the temperature of the flask is raised to 130–150°. When the residue in the flask is only 3–5 ml., the cyanogen chloride flow is discontinued and the distillation is stopped. This part of the reaction (from the start of the cyanogen chloride feed) requires about 0.4–0.6 mole of cyanogen chloride and takes about 0.75–1 hour.

The crude product, which may contain dissolved cyanogen chloride, is redistilled at a pressure of 100 mm. through the helices-packed column. Heating is done very slowly at first to allow the unreacted cyanogen chloride to distil and be condensed in the dry ice trap. The product is collected at 54–56° (100 mm.); d_4^{20} 1.626, weight 67.7–69.9 g. (60–62%) (Notes 9–11).

2. Notes

1. The lubricant for the ground-glass sleeve of the stirrer may be silicone oil or mineral oil; however, Teflon® oil is preferred. Glycerin should not be used.

2. The checkers used cyanogen chloride supplied in a metal cylinder by the American Cyanamid Co., Bound Brook, New Jersey. The submitter prepared cyanogen chloride beforehand² and either charged it as a liquid or allowed it to distil in as is required later in the reaction.³

3. The checkers used Sulfan®, a stabilized liquid form of sulfur trioxide which is commercially available from Baker and Adamson, General Chemical Division, Allied Chemical Corp., Morristown, New Jersey. The submitter distilled sulfur trioxide from 65% oleum directly into the reaction flask, a procedure which is described elsewhere.³

4. Chlorosulfonyl isocyanate reacts violently with water. For safety reasons, therefore, it is recommended that either air or dry ice mixtures be used for all cooling condensers and cooling baths. The dry ice may be mixed with methylene chloride. Acetone is not recommended, as chlorosulfonyl isocyanate may react with it.

5. Too much cooling in the early stages of the reaction may cause the cyanogen chloride to crystallize. Furthermore, if the

reaction mixture is cooled to substantially lower than -15° , *e.g.*, to -30° or -40° , the rate of reaction will decrease to the extent that there is danger of an uncontrollable delayed reaction.

6. At this point the reaction mixture may be stored protected from atmospheric moisture for an unlimited length of time before converting it to chlorosulfonyl isocyanate.

7. It is highly desirable to heat the distillation column with an electrical heating tape to compensate for heat loss. A 6 ft x $\frac{1}{2}$ in., 288-watt heating tape available from Briscoe Manufacturing Co., Columbus, Ohio, was used by the checkers. This should not be necessary when the reaction is conducted on a larger scale.

8. A flowmeter calibrated for use with air was used. Although this introduces some degree of error, it is adequate for the preparation.

9. The submitter conducted the reaction on ten times the scale indicated here and obtained yields of 88–93%. The checkers, however, on a scale of 0.80 mole, reproducibly obtained the lower yields indicated.

10. For storage over a short time, glass bottles sealed with rubber stoppers that are covered with polyethylene sheet are adequate. Ground-glass stoppers, even if thoroughly coated with silicone grease, will soon become frozen. For storage over moderate periods of time (several weeks) low-pressure polyethylene may be used. If traces of sulfur trioxide are present, the walls of the polyethylene vessel will soon become black; if more than 2% of cyanogen chloride is present, the polyethylene is attacked without a change in color, and its surface is converted to a crumbly mass. For storage over a long period of time, Teflon[®] FEP bottles available from the Nalge Co., Inc., Rochester, New York, or sealed-glass ampoules may be used.

11. Chlorosulfonyl isocyanate is a colorless, fluid liquid which fumes slightly in moist air. The vapors have a tussive effect. The compound shows an extraordinarily violent, almost explosive-like reaction with water. The contact of a small amount of the compound with the skin has no deleterious effect if it is rapidly removed by rinsing with plenty of water. Contacts which last longer than a few seconds may result in severe burns.

Cotton fabrics will char immediately on contact with the compound and produce a dense smoke. A specific toxic effect other than the purely cauterizing effect of the compound has not been observed by the submitter during the past 10 years.

3. Methods of Preparation

The present procedure corresponds to the method described earlier by Graf.³

4. Merits of the Preparation

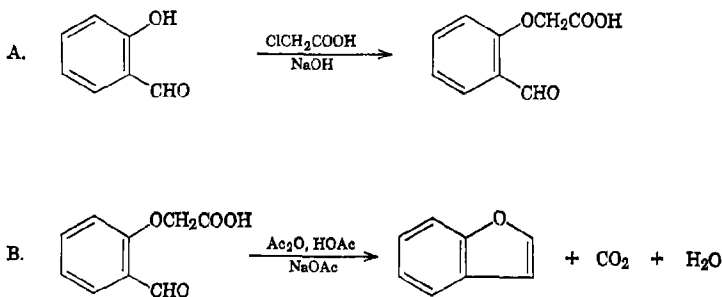
The cycloaddition of chlorosulfonyl isocyanate to olefins, followed by removal of the N-sulfonyl chloride group of the resulting β -lactam-N-sulfonyl chloride, offers a convenient synthesis of a large number of β -lactams unsubstituted on nitrogen.⁴⁻⁶ Also produced in the reaction with olefins are unsaturated carboxamide-N-sulfonyl chlorides, which, like the β -lactam-N-sulfonyl chlorides, may be worked up in various ways to give a variety of products.⁵⁻⁶ Chlorosulfonyl isocyanate reacts with aldehydes, e.g., benzaldehyde, to give imine-N-sulfonyl chlorides which will undergo cycloaddition reactions with ketene or dimethyl ketene to give, after removal of the sulfonyl chloride group, β -lactams also.⁵

Compounds containing active hydrogens react with chlorosulfonyl isocyanate first at the isocyanate group to give N-substituted sulfamyl chlorides which may react further with more active hydrogen compound at the sulfonyl chloride group.^{3, 7-10}

- 1 Farbwerke Hoechst AG, Frankfurt on the Main, Germany.
- 2 G. Brauer, ed., "Handbook of Preparative Inorganic Chemistry," 2nd ed., Academic Press, New York, 1963, Vol 1, pp 662-665, see also G. H. Coleman, R. W. Leeper, and C. C. Schulze, *Inorg. Syn.*, **2**, 90 (1946), H. Schroder, *Z. Anorg. Allgem. Chem.*, **297**, 296 (1958)
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5. R. Graf, *Ann.* **661**, 111 (1963)
- 6 H. Hoffmann and H. J. Diehr, *Tetrahedron Letters*, 1875 (1963).
7. R. Graf, *Ber.*, **92**, 509 (1959)
- 8 R. Graf, *Ber.*, **96**, 56 (1963)
9. German Patent 931,225 [*C. A.*, **50**, 7861 (1956)]
10. R. Appel and W. Senkpiel, *Ber.*, **91**, 1195 (1958).

COUMARONE

(Benzofuran)

Submitted by ALBERT W. BURGSTAHLER and LEONARD R. WORDEN¹Checked by WAYLAND E. NOLAND, WILLIAM E. PARHAM,
and CAROL WONG

1. Procedure

A. *o*-Formylphenoxyacetic acid. A solution of 80.0 g. (2 moles) of sodium hydroxide pellets in 200 ml. of distilled water is added to a mixture of 106 ml. (122 g., 1 mole) of salicylaldehyde (Note 1), 94.5 g. (1 mole) of chloroacetic acid (Notes 1 and 2), and 800 ml. of water. The mixture is stirred slowly and heated to boiling. The resulting black solution (Note 3) is heated under reflux for 3 hours (Note 4). The solution is acidified with 190 ml. of concentrated hydrochloric acid (sp. gr. 1.19) and is steam-distilled to remove unchanged salicylaldehyde (40.0–40.5 g.) (Note 5). The residual acidic mixture is cooled to 20°, and the precipitated product is collected on a Büchner funnel and rinsed with water. The light tan solid when dry weighs 99–100 g. (82–83% based on recovered salicylaldehyde), m.p. 130.5–133.0° (Note 6).

B. *Coumarone*. A mixture of 90.0 g. (0.5 mole) of crude (Note 7), dry *o*-formylphenoxyacetic acid, 180 g. of anhydrous, powdered sodium acetate, 450 ml. of acetic anhydride, and 450 ml.

of glacial acetic acid (Note 8) in a 2-l. flask is heated under gentle reflux with stirring for 8 hours. The hot black solution (total volume *ca.* 1.2 l.) (Note 3) is poured into 2.5 l. of ice water and extracted with one 600-ml. portion of ether (Note 9). The ether layer is washed with one 600-ml. portion of water and then with several portions of cold dilute 5% sodium hydroxide solution (Note 10) until the aqueous layer is basic. The ether layer is washed successively with water and saturated sodium chloride solution and is partially dried over anhydrous granular sodium sulfate. The ether is removed at water-bath temperature and the product is distilled, b.p. 166.5–168.0° (735 mm.) or 97.5–99.0° (80 mm.). The water-white benzofuran weighs 37.5–40.0 g. (63.5–67.8%, 52–56% overall from salicylaldehyde), n_D^{20} 1.5672; $\lambda_{\max}$ 245 (log ϵ 4.08), 275 (3.45), and 282 m μ (3.48).

2. Notes

1. Matheson, Coleman and Bell practical grade material was used.

2. The yield is not increased by use of bromoacetic acid or 2 moles of chloroacetic acid and an additional mole of sodium hydroxide.

3. At no time did the checkers observe a black solution. The color of the solution changed from yellow to red-brown.

4. The yield is not increased by longer reflux periods.

5. Removal of unchanged salicylaldehyde by steam distillation (followed conveniently by testing the distillate with 2,4-dinitrophenylhydrazine reagent) provides a product sufficiently pure for use in the next step. Also, the recovered salicylaldehyde can be used again without further purification.

6. Three crystallizations of 36 g. of the crude *o*-formylphenoxyacetic acid from 360 ml. of water with 10 g. of activated carbon give 18 g. of glistening colorless plates, m.p. 133.0°–133.5°.

7. Use of purified *o*-formylphenoxyacetic acid increases the yield in this step by only 11%.

8. If no acetic acid is used, benzofuran is formed in only 30–31% yield, and coumarilic acid, m.p. 194–196°, is isolated in about 45% yield.

9 An additional extraction does not increase the yield appreciably

10 About 250 ml of this solution is required.

3. Methods of Preparation

o-Formylphenoxyacetic acid has been prepared previously in 46% yield by alkylation of salicylaldehyde with chloroacetic acid ^{2, 3} and in unspecified yield by alkylation with ethyl bromoacetate followed by hydrolysis ⁴

Benzofuran is found in coal tar ⁵ It has been prepared in 40-46% overall yield from coumarin by bromination, conversion of the resulting 3,4-dibromocoumarin to coumarilic acid, and then decarboxylation, ⁶ and also by passage of coumarin vapor through an iron tube at 860° ⁷ The method given here is a variation of that described by Rossing, ² who omitted the addition of acetic acid (see Note 8 above). Benzofuran also has been prepared by the cyclization of ω chloro-*o*-hydroxystyrene ⁸ or phenoxyacetaldehyde ⁹ in unspecified low yields and by the cyclization of phenoxyacetaldehyde diethyl acetal in 9% yield. ¹⁰ High temperature catalytic dehydrocyclization of *o*-ethylphenol affords benzofuran in as much as 59% yield after recycling unchanged *o*-ethylphenol ¹¹

4. Merits of the Preparation

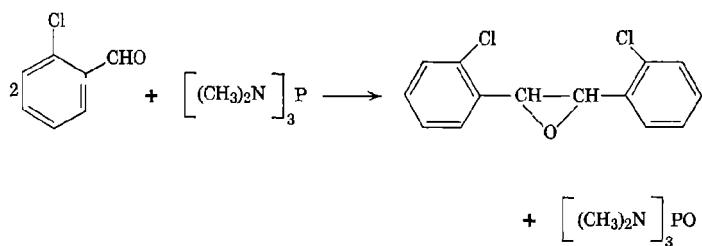
Although the high-temperature catalytic dehydrocyclization of *o*-ethylphenol ¹¹ gives benzofuran in fair yield, these conditions are not convenient in the laboratory and cannot be applied easily to functionally substituted *o*-formylphenoxyacetic acids. The other methods of preparation give unsatisfactory yields, are unnecessarily lengthy, or require expensive starting materials. The method of Rossing, ² on which the present procedure is based, gives good yields in its original form only in the case of *o*-acylphenoxyacetic acids; *o*-formylphenoxyacetic acids give principally the corresponding coumarilic acids. Often these can be decarboxylated only in very poor yield ¹² In the preparation described here, benzofuran is obtained directly in fair overall

yield from readily available and inexpensive starting materials without the necessity of a separate decarboxylation step.

- 1 Department of Chemistry, University of Kansas, Lawrence, Kansas This investigation was supported in part by a Public Health Service Fellowship, GPM 13, 681 03 from the Division of General Medical Sciences, U S Public Health Service
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- 4 H Dumont and St v Kostanecki, *Ber*, **42**, 911 (1909)
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- 7 N A Orlow and W W Tistschenko, *Ber*, **63**, 2948 (1930)
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- 9 R Stoermer, *Ber*, **30**, 1700 (1897)
- 10 R Stoermer, *Ann*, **312**, 237 (1900)
- 11 C Hansch and G Helmkamp, *J Am Chem Soc*, **73**, 3080 (1951), and earlier papers cited therein, B B Corson, H E Tiefenthal, J E Nickels, and W J Heintzelman, *J Am Chem Soc*, **77**, 5428 (1955)
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2,2'-DICHLORO- α,α' -EPOXYBIBENZYL

(Bibenzyl, α,α' -epoxy-, 2,2'-dichloro-)



Submitted by V MARK¹

Checked by G A FRANK and W D EMMONS

1. Procedure

To a solution of *o*-chlorobenzaldehyde (56.2 g., 0.4 mole) (Note 1) in 50 ml. of benzene in a 250-ml. three-necked flask

equipped with a stirrer, thermometer, dropping funnel, and reflux condenser, there is added a solution of hexamethylphosphorous triamide (37.9 g., 0.232 mole) in 20 ml. of dry ether² at such a rate that the temperature remains between 24° and 36°. The ensuing exothermic reaction is controlled readily by immersing the flask in a water bath (Note 2). After completion of the addition, which requires 30–50 minutes, the clear solution is maintained at 50° for 15 minutes. The solvent is removed on a rotary evaporator, and the oily residue is triturated with 100 ml. of water and then with 150 ml. of pentane. At this point only a small portion of the product is left undissolved (Note 3). The aqueous layer is extracted with 150 ml. of pentane (Note 4). The combined pentane solution is washed with two 100-ml. portions of water and concentrated to dryness to give 46–50 g. of a light yellow solid. Recrystallization from 100 ml. of methanol yields 37.5–43.1 g. of white crystals (71–81%), composed of a mixture of the *trans* epoxide (about 50–55%) and the *cis* epoxide (about 45–50%) (Notes 5, 6, 7).

2. Notes

1. The commercial product was distilled before use. The checkers found the undistilled material equally satisfactory.

2. The solvent can be omitted, but more efficient cooling is then required to control the reaction.

3. Pentane dissolves the epoxide and water dissolves the co-product, hexamethylphosphoric triamide. The insoluble, thick, yellow syrup sometimes found is the betaine 1:1 adduct of the aldehyde and amide.³ The checkers found no insoluble portion in their preparations.

4. Filtration through a sintered-glass funnel readily breaks up the emulsion which is formed occasionally.

5. The simplest and most accurate way to determine the composition of the product is by proton n.m.r. spectroscopy. The ratio of the oxirane hydrogen atoms (*cis* 4.48 p.p.m. and *trans* 3.97 p.p.m. downfield from internal tetramethylsilane reference, determined in carbon tetrachloride or deuteriochloroform solution)³ gives directly the ratio of the isomers. Infrared

spectroscopy, although it readily distinguishes between the isomers, gives a less accurate quantitative relationship.

6. Chromatography over alumina, using pentane as eluent, yields pure *trans*-epoxide (m.p. 72–74°) in the first fractions. The isolation of the *cis* isomer is more difficult, and prolonged elution is necessary.

7. Hexaethylphosphorous triamide² may be substituted for the methyl homolog without adverse effect on the quality and yield of the product.

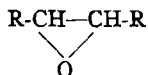
3. Methods of Preparation

2,2'-Dichloro- α,α' -epoxybibenzyl has been prepared only by the present procedure.³

4. Merits of the Preparation

The reaction of aldehydes with hexaalkylphosphorous triamides to yield the corresponding epoxides is a synthetic procedure of considerable scope (Table I) and represents a new and simple,

TABLE I
SYNTHESIS OF SYMMETRICAL EPOXIDES



R	% Yield	Composition	
		% <i>trans</i>	% <i>cis</i>
<i>o</i> -Bromophenyl	90–95	59	41
<i>m</i> -Bromophenyl	45–50	72 ^a	28
<i>o</i> -Fluorophenyl	90–95	60	40
3,4-Dichlorophenyl	88–95	60	40
<i>m</i> -Nitrophenyl	75–80	74 ^b	26
<i>p</i> -Cyanophenyl	90–95	57	43
<i>p</i> -Formylphenyl	75–80	53	47
1-Naphthyl	83–87	53	47
2-Thienyl ^c	60–65	53	47
2-Pyridyl	85–90	75 ^d	25

^aM.p. 84–86°.

^bM.p. 156–158°.

^cHexaethylphosphorous triamide was used.

^dM.p. 95–97°.

one-step method of forming symmetrical and unsymmetrical epoxides.³ In contrast to the most widely used epoxide synthesis, *i.e.*, from olefins with peroxides or peracids, the present procedure may be used to obtain epoxides having structural features (*e.g.*, thiophene or pyridine rings) which would not survive the more drastic peroxide route. The procedure does not, however, afford stereochemically unique products. The yields of the epoxides from the corresponding aldehydes are usually high, and new members of the underpopulated class of aromatic and heterocyclic epoxides become readily accessible. Application of this method to certain aromatic dialdehydes yielded the first examples of cyclic aromatic epoxides.⁴

1 Hooker Chemical Corporation, Niagara Falls, New York

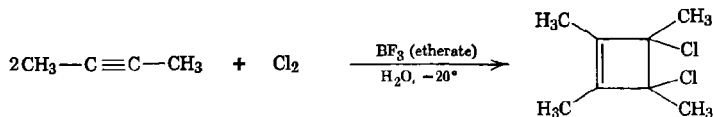
2 V Mark, *Org Syntheses*, this volume, p 42

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4 M S Newman and S Blum, *J Am Chem Soc*, **86**, 5598 (1964)

3,4-DICHLORO-1,2,3,4-TETRAMETHYLCYCLOBUTENE

(Cyclobutene, 1,2,3,4-tetramethyl-3,4-dichloro-)



Submitted by R. CRIEGEE¹

Checked by G. BROWN and V. BOEKELHEIDE

1. Procedure

A 400-ml. three-necked flask equipped with a mechanical stirrer, a gas dispersion tube, and a thermometer is charged with 216 g. (4 moles) of 2-butyne, 14 ml. of boron trifluoride etherate, and 1 ml. of water. The mixture is stirred vigorously while the flask is partially immersed in a dry ice-acetone bath to maintain an internal temperature of -20° . Chlorine (195 g., 2.75 moles) is then added (Note 1) gradually over a period of 17–20 hours.

When all the chlorine has been added, the flask and contents (Note 2) are cooled to -78° and held at this temperature for 30 minutes. The white crystalline product which separates is collected on a sintered-glass funnel, 160–170 g. (45–48%) of crude crystals, m.p. $53-55^{\circ}$, is obtained. The crude product when cooled at -20° takes on a reddish or blue color after a few days (Note 3).

Purification of the crude material is accomplished by dissolving it in petroleum ether ($30-50^{\circ}$) or methylene chloride, shaking this solution three times with water, and passing the organic layer through a fluted filter paper. After the filtrate has been dried over anhydrous sodium sulfate, it is concentrated to a small volume and cooled to -78° . The perfectly white, crystalline product which separates is collected yielding 110–120 g. (30–33%) of crystals, m.p. $57-58^{\circ}$ (Note 4).

2. Notes

1. The chlorine is most conveniently added by liquefying the required amount in a gas trap. The gas trap is placed in an empty Dewar flask and covered with glass wool. While the liquid chlorine slowly warms up, the resulting gaseous chlorine is passed through a sulfuric acid wash bottle into the reaction mixture. The addition generally takes 17–20 hours.

2. The final reaction mixture is slightly yellow, but at times it can be reddish. During the reaction some white crystalline product collects at the walls of the reaction vessel.

3. It is important to purify the crude product as soon as possible since it decomposes readily in the impure state. Once decomposition has set in, purification is difficult.

4. A still purer product is obtained if the dried petroleum ether solution is evaporated to dryness with a water aspirator and the residual crude product distilled through a Vigreux column. After a small fore-run, pure tetramethyl-3,4-dichlorocyclobutene distills at $59-60^{\circ}$ at 12 mm. The product melts at 58° and is more stable at room temperature than the recrystallized but undistilled material.

3. Methods of Preparation

The method used is that of Criegee and Moschel² Smirnow-Samkow³ made the same substance by the reaction of 2-butyne with sulfuryl chloride in 10-15% yield.

4. Merits of the Preparation

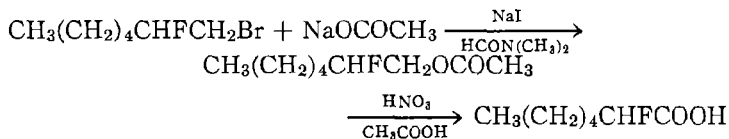
3,4-Dichloro-1,2,3,4-tetramethylcyclobutene is an unusually versatile intermediate.⁴ The tertiary and allylic chlorine atoms undergo ready solvolysis. With lithium aluminum hydride the chlorine atoms are replaced by hydrogen. The resulting *cis,trans*-tetramethylcyclobutenes are starting materials for numerous transformations, *e.g.*, thermolysis leads to stereoisomeric tetramethylbutadienes.⁵ Lithium amalgam in ether results in the formation of octamethyltricyclooctadiene. With nickel carbonyl the nickel chloride complex of tetramethylcyclobutadiene is formed.⁶ Ammonia transforms the dichloride into tetramethylpyrrole.⁷ Other reactions have been reported.⁸

This method of preparation is simpler, more reproducible, and gives considerably better yields than the original one of Smirnow-Samkow.

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2-FLUOROHEPTANOIC ACID

(Heptanoic acid, 2-fluoro-)

Submitted by F H DEAN, J H AMIN, and F L M PATTISON¹

Checked by MICHELLE MORAN and B C MCKUSICK

1. Procedure

A. *2-Fluoroheptyl acetate* A 1-l. two-necked flask is fitted with a thermometer reaching close to the bottom and a reflux condenser that has a calcium chloride tube in its end. It is charged with 29.6 g. (0.150 mole) of 1-bromo-2-fluoroheptane,² 22.5 g. (0.150 mole) of dry sodium iodide, 24.6 g. (0.30 mole) of anhydrous sodium acetate, and 600 ml. of dimethylformamide previously dried over anhydrous calcium sulfate. The mixture is stirred by a magnetic bar for 40 hours while being maintained at 120–130° by means of an electric heating mantle. The mixture is cooled to room temperature, diluted with 750 ml. of water, and extracted with 900 ml. of ether. The aqueous layer is extracted with two 150-ml. portions of ether, and the combined ether extracts are washed with five 150-ml. portions of water (Note 1). The ethereal solution is dried over anhydrous sodium sulfate. The ether is removed by distillation, and the residue is transferred to a Claisen flask with a 15-cm. indented neck. Fractionation under reduced pressure gives, after a small fore-run, 16.6–20.6 g. (63–78%) of 2-fluoroheptyl acetate, b.p. 83–87° (10 mm.), n_D^{25} 1.4101.

B. *2-Fluoroheptanoic acid* (Note 2) A 250-ml. two-necked flask is fitted with a thermometer and a condenser that has an outlet tube to carry oxides of nitrogen to a gas absorption trap³ or the back of a hood. It is charged with 17.6 g. (0.100 mole) of

2-fluoroheptyl acetate, 50 ml. of glacial acetic acid, and 60 ml of 16 *N* nitric acid. The mixture is heated at 48–50° for 25 hours by means of an electric heating mantle. It is diluted with 500 ml of water and crushed ice and extracted with one 300-ml portion and five 100-ml portions of ether (Note 3). The combined ether extracts are added carefully to a slurry of 125 g of sodium bicarbonate in 500 ml of water in a 2-l. beaker. The aqueous alkaline solution is extracted with two 100-ml. portions of ether, which are discarded. The aqueous solution is neutralized to a pH of approximately 4 with about 300 ml. of 10% hydrochloric acid and is extracted with one 300 ml. portion and five 100-ml portions of ether. The combined extracts are washed with four 100-ml portions of water to remove traces of acetic acid and dried over anhydrous sodium sulfate. The ether is removed by distillation, leaving 12–13.5 g. of crude 2-fluoroheptanoic acid that soon solidifies. It is purified by distillation under reduced pressure through a short Claisen still-head with a short condenser that can be heated by steam, a burner, or a heat lamp when the acid solidifies in it. 2-Fluoroheptanoic acid, b p 62–64° (0.15 mm.), 78–80° (0.7 mm.), is obtained as a moist, waxy, pale yellow solid that smells faintly of acetic acid. After being dried on a porous plate, it is odorless and nearly colorless, weight 11.5–12.5 g. (78–84%), m p. 38–39°.

2. Notes

1 Thorough washing with water is necessary to remove residual dimethylformamide.

2 2-Fluoroheptanoic acid required no more than the usual precautions accorded organic compounds, for it and its precursors have $LD_{50} > 100$ mg/kg in mice. The relatively low toxicity of this and other 2-fluoroalkanoic acids is in contrast to the high toxicity of the ω -fluoro acids $F(CH_2)_nCOOH$ with n an odd number (if $n = 5$, $LD_{50} = 1.3$ mg./kg in mice).⁴

3 The solubility of the fluoro acid in water is sufficient to require thorough ether extraction.

3. Methods of Preparation

2-Fluoroheptanoic acid⁵ has been prepared only by the present procedure

4. Merits of the Preparation

Bromofluorination² followed by the present procedure is a general way to convert 1 alkenes to 2-fluoroalkanoic acids; similar results have been obtained with ethylene, propylene, 1-butene, 1-hexene, 1-octene, 1-decene, and methyl 10-undecenoate.⁵ It is an easy and convenient way to make 2-fluoroalkanoic acids, for it requires only conventional apparatus and readily available intermediates.

1 Department of Chemistry, University of Western Ontario, London, Ontario, Canada

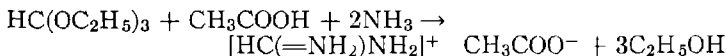
2 F H Dean, J H Amin, and F L M Pattison, *Org Syntheses*, this volume, p 10

3 C F H Allen, *Org Syntheses*, Coll Vol 2, 4 (1943)

4 F L M Pattison, S B D Hunt, and J B Stothers, *J Org Chem*, **21**, 883 (1956)

5 F L M Pattison, R L Buchanan, and F H Dean, *Can J Chem*, **43**, 1700 (1965)

FORMAMIDINE ACETATE



Submitted by EDWARD C TAYLOR, WENDELL A EHRHART, and M KAWANISI¹

Checked by JOHN J MILLER and WILLIAM D EMMONS

1. Procedure

In a 500-ml. three-necked flask equipped with a reflux condenser, a gas-inlet tube (Note 1) reaching to the bottom of the flask, a thermometer, and a magnetic stirrer is placed a mixture of 90.0 g. of triethyl orthoformate (Note 2) and 49.2 g. of glacial acetic acid. The flask is immersed in an oil bath maintained at 125–130° (Note 3). When the internal temperature of the mixture reaches 115°, a moderate stream of ammonia is introduced.

As the temperature decreases gradually, vigorous refluxing is observed (Note 4). Formamidine acetate starts to crystallize from the boiling mixture after 20–30 minutes. The ammonia flow is continued until no further decrease in temperature is observed (Note 5). The mixture is cooled to room temperature, the precipitate collected by filtration and washed thoroughly with 50 ml. of absolute ethanol. The yield of colorless formamidine acetate is 53.0–55.8 g. (83.8–88.2%), m.p. 162–164° (Note 6). Evaporation of the mother liquor under reduced pressure followed by chilling gives a small additional amount of product (1.0–2.2 g.) (Note 7).

2. Notes

1. An open-end gas-inlet tube should be used rather than a fritted glass inlet because the latter becomes clogged.

2. Commercial triethyl orthoformate, b.p. 50–52° (20 mm.) (Matheson, Coleman and Bell) is used without further purification.

3. If the temperature is higher than 140°, the product is colored and the yield is lower.

4. This temperature decrease serves as a useful indication of the progress of the reaction.

5. The final temperature of the reaction mixture is usually 72–73°. Total working time is 60–70 minutes.

6. Recrystallization from ethanol does not change the melting point.

7. This material is usually slightly colored and not so pure as the first crop.

3. Methods of Preparation

This method is a modification of the procedure described by Taylor and Ehrhart.² Formamidine has previously been prepared (as its hydrochloride) from hydrogen cyanide via the formimino ether, which is then treated with ammonia,³ or by desulfurization of thiourea in the presence of ammonium chloride.⁴ The methosulfate salt of formamidine has been reported to be formed by reaction of formamide with dimethyl sulfate.⁵

4. Merits of the Procedure

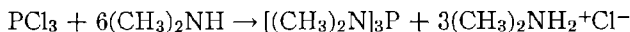
Because formamidine hydrochloride is extremely deliquescent, considerable care must be exercised in its preparation if satisfactory results are to be achieved. Furthermore, formamidine hydrochloride cannot be used directly in most condensation reactions; it must be treated first with a mole of base to liberate free formamidine. The same restriction applies to the methosulfate salt of formamidine; in addition, complications in synthesis may be anticipated in this latter case because methyl hydrogen sulfate itself is an effective methylating agent.⁶

By contrast, formamidine acetate is not hygroscopic and no particular care need be taken to protect it from atmospheric moisture. Furthermore, formamidine acetate can be used directly without prior treatment with base in syntheses requiring free formamidine.^{2, 7-10} Finally, this preparation of formamidine is by far the simplest and most convenient yet reported; it obviates the necessity of using either toxic (hydrogen cyanide) or cumbersome (Raney nickel) reagents, and the method can be adapted to the preparation of N,N'-disubstituted formamidines by substitution of primary amines for ammonia.¹¹

1. Department of Chemistry, Princeton University, Princeton, New Jersey.
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3. A. Pinner, *Ber.*, **10**, 352, 1643 (1883).
4. D. J. Brown, *J. Appl. Chem.*, **2**, 202 (1952).
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11. E. C. Taylor and W. A. Ehrhart, *J. Org. Chem.*, **28**, 1108 (1963).

HEXAMETHYLPHOSPHOROUS TRIAMIDE

(Phosphorous triamide, hexamethyl-)



Submitted by V. MARK¹

Checked by G. A. FRANK and W. D. EMMONS

1. Procedure

A solution of phosphorus trichloride (137.3 g., 1.0 mole) in 1.5 l. of dry ether (Note 1) is added to a 3-l., three-necked, round-bottomed flask equipped with an efficient stirrer, thermometer, a gas-inlet tube (Note 2), and a reflux condenser vented through a nitrogen reservoir (a T-tube under slight positive nitrogen pressure) into a well-functioning hood (Note 3). The flask is cooled in an ice bath to 0–5°, and an excess of anhydrous dimethylamine (Note 4) is introduced at such a rate that the temperature does not exceed 15°. The addition requires about 3–4 hours. At the end of this period the flask contains the white stirrable slurry of the amine hydrochloride and the ethereal solution of the phosphorous triamide (Note 5). The reaction mixture is allowed to warm to room temperature overnight while still being protected by nitrogen. Filtration of the slurry and thorough washing of the filter cake with three 100-ml. portions of dry ether afford dimethylamine hydrochloride, quantitatively (Note 6). The clear filtrate is concentrated on a rotary evaporator connected to a water aspirator in a bath not exceeding 40° to give 152–154 g. (94–95%) of hexamethylphosphorous triamide as a light yellow oil. The product can be purified by distillation at atmospheric pressure, b.p. 162–4°, or under reduced pressure, b.p. 49–51° (12 mm.), n_D^{25} 1.4636 (Note 7). Hexamethylphosphorous triamide is best stored in a nitrogen atmosphere (Note 8).

2. Notes

1. An equal volume of a hydrocarbon solvent (pentane, hexane, benzene) can be substituted for ether without affecting the yield of the triamide.

2. The lower part of the gas-inlet tube, which reaches below the surface of the liquid, should be wide enough that it will not be clogged by the amine hydrochloride. A 12-mm. I.D. glass tube was found satisfactory.

3. Carbon dioxide is not satisfactory because it reacts with hexamethylphosphorous triamide.

4. Available from the Matheson Company. The checkers used Rohm & Haas anhydrous dimethylamine.

5. The water extract of the clear solution should give, after acidification with dilute nitric acid, no white precipitate with silver nitrate. When free of chloride ion, the water extract gives only a dark coloration or precipitate.

6. The use of a large (9.5 cm. in diameter, 8 cm. high or larger), coarse grade, sintered-glass funnel, which permits the slurring and thorough rinsing of the filter cake, is recommended. Since the conversion of the phosphorus trichloride to the triamide is quantitative, the major cause of lower yields is the retainment of the liquid product by the salt cake.

7. As a safety precaution the exposure of the hot material in the flask to air should be avoided. The checkers recovered 134 g. (82%) of distillate from 153 g. of crude product.

8. Essentially the same procedure can be used to obtain the higher alkyl homologs of hexamethylphosphorous triamide. Since the higher dialkylamines are liquid at room temperature, the gas-inlet tube is replaced by an addition funnel. Alternatively, the mode of addition may be reversed (*i.e.*, phosphorus trichloride may be added to the amine) without affecting the subsequent workup or yield. The higher homologs of hexamethylphosphorous triamide such as the ethyl, *n*-propyl, and *n*-butyl can also be prepared in 95–100% conversion when a slight excess (5–10%) of the amine is employed.

3. Methods of Preparation

The described procedure is a modification of the method of Carmody and Zletz² and of Burg and Slota.³ The higher homologs were reported by Stuebe and Lankelma.⁴

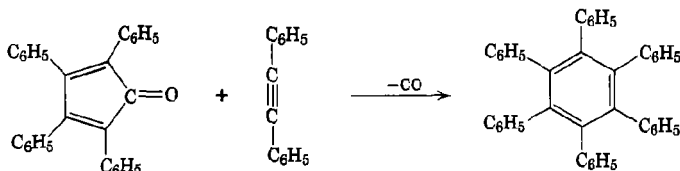
4. Merits of the Preparation

This is a general method of preparing hexaalkylphosphorous triamides from the corresponding dialkylamines. The procedure is simple, and the yields are high. Hexaalkylphosphorous triamides are powerful nucleophiles.⁵ This feature can be used in a rather unique way to synthesize epoxides directly from aldehydes.^{5, 6}

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2. D. R. Carmody and A. Zletz, U.S. Patent 2,898,732 (1959).
3. A. B. Burg and P. J. Slota, Jr., *J. Am. Chem. Soc.*, **80**, 1107 (1958).
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HEXAPHENYLBENZENE

(Benzene, hexaphenyl-)



Submitted by LOUIS F. FIESER¹

Checked by CHESTER E. RAMEY and V. BOEKELHEIDE

1. Procedure

A 100-ml., round-bottomed, ground-glass flask containing 40 g. of benzophenone is heated over a free flame to melt the bulk of the solid, and then 8.0 g. of tetraphenylcyclopentadienone (0.021

mole) (Note 1) and 8.0 g. of diphenylacetylene (0.043 mole) (Note 2) are introduced through a paper cone so that no material lodges on the neck or walls. An air condenser is attached, and the mixture is heated over a microburner so that it refluxes briskly but without flooding the condenser (the temperature of the liquid phase is 301–303°). Carbon monoxide is evolved, the purple color begins to fade in 15–20 minutes, and the color changes to a reddish brown in 25–30 minutes. When no further lightening in color is observed (after about 45 minutes), the burner is removed and 8 ml. of diphenyl ether is added to prevent subsequent solidification of the benzophenone. The crystals that separate are brought into solution by reheating, and the solution is let stand for crystallization at room temperature. The product is collected and washed free of brown solvent with benzene to give 9.4 g. (84%) of colorless plates, m.p. 454–456° (sealed capillary) (Note 3). A satisfactory solvent for recrystallization is diphenyl ether, using 7 ml. per gram of product.

2. Notes

1. A synthesis of tetraphenylcyclopentadienone is described in *Org. Syntheses*, Coll. Vol. 3, 806 (1955). However, the following procedure is more convenient. A 250-ml. Erlenmeyer flask is charged with 21 g. of benzil, 21 g. of dibenzyl ketone (Eastman Organic Chemicals, practical grade), and 100 ml. of triethylene glycol, a thermometer is introduced, and the mixture is heated over a free flame until the solid has dissolved. A 10-ml. portion of a 40% solution of benzyltrimethylammonium hydroxide in methanol is made ready, the temperature of the reaction mixture is adjusted to 100°, the basic catalyst is added, and the mixture is swirled once for mixing and let stand. Within 15–20 seconds the liquid sets to a stiff paste of purple crystals and the temperature rises to 115°. After the temperature has dropped to 80°, the mixture is cooled, thinned by stirring in 50 ml. of methanol, and the product is collected and washed with methanol until the filtrate is purple, not brown. The yield of product, m.p. 219–220°, is 35.5 g. (93%). Recrystallization can be accomplished

with 92% recovery by dissolving the ketone in triethylene glycol (10 ml./gram) at 220°.

2. Improvements in the preparation and dehydrohalogenation of *meso*-stilbene dibromide [*Org. Syntheses*, Coll. Vol. **3**, 350 (1955)] are as follows. *trans*-Stilbene (20 g.) is heated with 400 ml. of acetic acid on the steam bath until dissolved, 40 g. of pyridinium bromide perbromide is added, and the mixture is heated on the steam bath and swirled for 5 minutes. *meso*-Stilbene dibromide separates at once in pearly white plates. The mixture is cooled to room temperature, and the product is collected and washed with methanol. The yield of dibromide, m.p. 236–237°, is 32.4 g. (86%). A 250-ml., round-bottomed, ground-glass flask is charged with 32.4 g. of the dibromide, 65 g. of potassium hydroxide pellets, and 130 ml. of triethylene glycol. A 15 x 125 mm. test tube containing enough of the same solvent to cover the bulb of a thermometer is inserted in the flask. The flask is supported in a clamp, which is used as a handle for swirling the flask over a free flame to mix the contents and bring the temperature to 160°, when potassium bromide begins to separate. By intermittent heating and swirling the mixture is kept at 160–170° for 5 minutes more to complete the reaction. The test tube is then removed, dipped into 500 ml. of water in a beaker, and the adhering organic material is rinsed into the beaker with 95% ethanol. The hot reaction mixture is poured into the beaker, and the flask is rinsed alternately with water and with ethanol. After cooling, the crude product is collected, washed with water, and air-dried (16.5 g.). The brown solution of this material in 50 ml. of 95% ethanol is filtered from a little dark residue, reheated, and let stand for crystallization. A first crop of diphenylacetylene (11.8 g.) separates in large colorless spars, m.p. 61.5–62.5°. Concentration of the mother liquor yields an additional 2.4 g. of crystals, m.p. 58–59°.

The checkers used diphenylacetylene provided by Aldrich Chemicals.

3. The melting point is determined conveniently with a Mel-Temp apparatus and a 90–510° thermometer designed for use with it (Laboratory Devices, Post Office Box 68, Cambridge 39, Massachusetts). An evacuated capillary containing a sample is

sealed close to the sample to prevent sublimation, and repeated determinations are made with the same sample. The figure 456° is the average of two determinations of the temperature of melting; 454° is the average of two observations of the point of solidification. When the amount of diphenylacetylene was reduced to 1.2 times the theory, the yield was the same but the melting point was $450\text{--}452^{\circ}$.

3. Methods of Preparation

Hexaphenylbenzene has been prepared by heating tetraphenylcyclopentadienone and diphenylacetylene without solvent² and by trimerization of diphenylacetylene with bis-(benzonitrile)-palladium chloride and other catalysts.³

4. Merits of the Preparation

Hexaphenylbenzene can be prepared satisfactorily by strong heating of a mixture of 0.5 g. each of tetraphenylcyclopentadienone and diphenylacetylene in a test tube, but the method is unsatisfactory on a larger scale because of the high melting point of the product and the poor heat transfer in a flask. The present procedure demonstrates use of benzophenone as solvent for a Diels-Alder reaction requiring a temperature of about 300° . When the reaction is completed, addition of a small amount of diphenyl ether lowers the melting point of benzophenone sufficiently to prevent this solvent from solidifying.

Other solvents tried and the liquid temperatures of the refluxing mixtures are: stearic acid ($340\text{--}365^{\circ}$), di-*n*-butyl phthalate ($320\text{--}325^{\circ}$), phenyl salicylate (290°). The first two solvents are unsatisfactory because of side reactions consuming some of the tetraphenylcyclopentadienone, the third because the addition reaction is too slow.

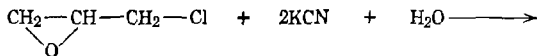
Note 1 describes an improvement in the preparation of the starting dienone involving use of a medium of higher solvent power and higher boiling point than ethanol and of a basic catalyst more convenient than potassium hydroxide because it is miscible with the solvent employed. Note 2 reports two im-

provements in the preparation of diphenylacetylene. The yield in the conversion of *trans*-stilbene to the *meso* dibromide is increased by use of the highly stereoselective reagent pyridinium bromide perbromide. In the dehydrohalogenation step the reaction time is reduced substantially and the yield increased by use of a high-boiling alcohol in place of ethanol.

1. Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138.
2. W. Dilthey and G. Hurtig, *Ber.*, **67**, 2007 (1934).
3. A. T. Blomquist and P. M. Maitlis, *J. Am. Chem. Soc.*, **84**, 2329 (1962).

3-HYDROXYGLUTARONITRILE

(Glutaronitrile, 3-hydroxy-)



Submitted by F. JOHNSON and J. P. PANELLA¹

Checked by A. G. ANASTASSIOU and B. C. MCKUSICK

1. Procedure

A mixture of 493 g. (2.00 moles) of magnesium sulfate heptahydrate and 700 ml. of tap water is stirred for 5 minutes and filtered into a 2-l. three-necked flask equipped with a mechanical stirrer and an alcohol thermometer that dips into the solution. The flask is immersed in a cooling bath (Note 1), the stirrer is started, and the solution is cooled to 10°. To the solution is added, in one portion, 143 g. (2.20 moles) of potassium cyanide (*Caution! Toxic*), and the stirring is continued for 45 minutes at 8–12° (Note 2). The solution is maintained at this temperature while 102 g. (1.10 moles) of epichlorohydrin (Note 3) is added dropwise with stirring over a period of 1 hour (Note 4). The mixture is allowed to come to room temperature and is stirred for an additional 24 hours at this temperature.

The dark red-brown reaction mixture is stirred and extracted continuously with 1 l. of ethyl acetate for 48 hours (Note 5). The

extract is dried over anhydrous magnesium sulfate for 18 hours (Note 6), filtered, and the filtrate is concentrated under reduced pressure on a steam bath. The residual dark-brown oil (about 90 g.) is distilled from a Claisen flask; the distillation must be rapid to minimize decomposition. About 20 g. of fore-run consisting of 4-chloro-3-hydroxybutyronitrile and 4-hydroxycrotononitrile is collected at 90–115° (0.4 mm.). 3-Hydroxyglutaronitrile is collected at 155–160° (0.4 mm.), yield 65–75 g. (54–62%), n_{D}^{23} 1.4634. This pale yellow distillate is sufficiently pure for most purposes. Further purification can be effected with only 3–5% loss by distillation of the material through a 15-cm. Vigreux column and collection of the portion boiling at 154–156° (0.2 mm.), n_{D}^{23} 1.4632 (Note 7).

2. Notes

1. The bath contained a mixture of trichloroethylene and solid carbon dioxide kept at -20° .

2. At this point the mixture has an opaque milky-white appearance caused by precipitation of a little magnesium hydroxide.

3. Epichlorohydrin (white label brand) supplied by Eastman Organic Chemicals was used without further purification.

4. The reaction is exothermic. If the temperature of the reaction mixture is allowed to rise above 30° , the reaction is likely to get out of control.

5. The checkers found that a stirred extractor² was much more efficient than an unstirred one for this operation.

6. This extensive drying period is necessary to allow precipitation of traces of basic salts that have been carried over during the extraction procedure. Failure to remove these salts results in extensive decomposition of the product during the distillation step.

7. The submitters have obtained the same yield working on 10 times this scale.

3. Methods of Preparation

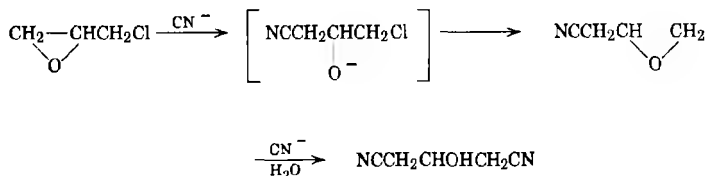
3-Hydroxyglutaronitrile has been prepared by the action of potassium cyanide on 1,3-dichloro-2-propanol³⁻⁵ or on 4-chloro-

3-hydroxybutyronitrile.^{6 7} More recently it has been prepared from epichlorohydrin using essentially the present method.⁸

4. Discussion

This is a much more convenient and satisfactory synthesis of 3-hydroxyglutaronitrile than earlier ones.³⁻⁷ The method can be applied to other epichlorohydrins; 2-methylepichlorohydrin and 2-ethylepichlorohydrin have been converted to the corresponding hydroxydinitriles in 71% and 77% yields, respectively.⁸ The hydroxydinitriles undergo cyclizations to heterocyclic compounds not easily prepared in other ways. Thus hydrogen bromide at 0° converts 3-hydroxyglutaronitrile to 2-amino-6-bromopyridine in 70% yield.⁹

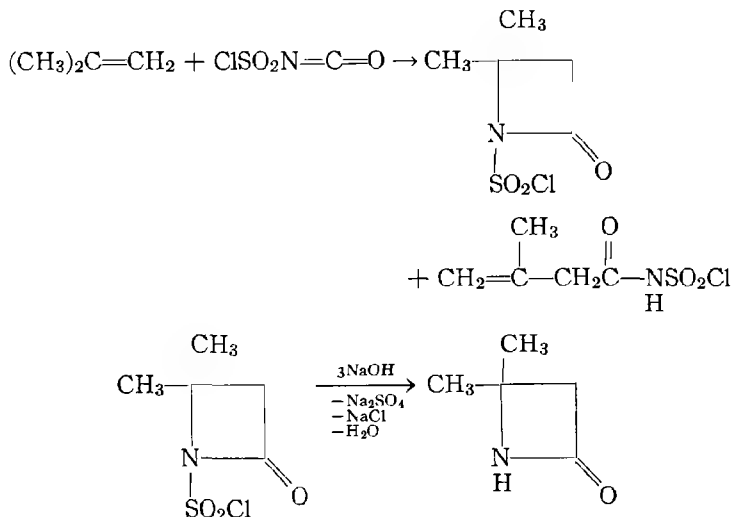
The reaction probably proceeds as follows:⁸



- 1 The Dow Chemical Company, Eastern Research Laboratory, Wayland, Massachusetts
- 2 G Billek, *Org Syntheses*, **43**, 49 (1963)
- 3 M Simpson, *Ann*, **133**, 74 (1865)
- 4 O Morgenstern and E Zerner, *Monatsh*, **31**, 777 (1910)
- 5 G Braun, *J Am Chem Soc*, **52**, 3167 (1930)
- 6 R Lespieau, *Bull Soc Chim France*, [4] **33**, 725 (1923)
- 7 R Legrand, *Bull Soc Chim Belges*, **53**, 166 (1944)
- 8 F Johnson, J P. Panella, and A A Carlson, *J Org Chem*, **27**, 2241 (1962)
- 9 F Johnson, J P Panella, A A Carlson, and D H Hunneman, *J Org Chem*, **27**, 2473 (1962).

**β -ISOVALEROLACTAM-N-SULFONYL CHLORIDE
AND β -ISOVALEROLACTAM**

(2-Azetidinone-4,4-dimethyl-1-sulfonyl chloride and
2-azetidinone-4,4-dimethyl)



Submitted by RODERICH GRAF¹

Checked by JEROME F. LEVY and WILLIAM D. EMMONS

1. Procedure

Caution! Chlorosulfonyl isocyanate is highly corrosive and may be contaminated with cyanogen chloride. This preparation should be carried out in a good hood, and rubber gloves should be worn.

A. β -Isovalerolactam-N-sulfonyl chloride. A 200-ml. four-necked flask fitted with a mechanical stirrer, a dry ice-jacketed dropping funnel (Note 1), and a thermometer is cooled with a dry ice-methylene chloride slush bath while 67 ml. of sulfur dioxide (Note 2) is condensed into the flask. Both the dry ice condenser and the dropping funnel are protected with drying

tubes containing anhydrous calcium sulfate. With the liquid sulfur dioxide at -20° , the flask is charged with 0.3 g. of finely powdered potassium chloride (Note 3) and 47.1 g. (0.33 mole) of chlorosulfonyl isocyanate.² Then 19.5 g. (0.35 mole) of isobutylene, previously condensed in a cold trap, is added to the dropping funnel. The temperature of the flask is lowered to -40° to -50° , and isobutylene is added dropwise over a 20-minute period (Notes 4, 5). After the isobutylene addition is completed, the cooling bath under the flask is removed, and the reaction mixture is allowed to warm up until the solvent begins to reflux (approximately -6°). The colorless contents of the flask are then poured into 125 ml. of water contained in a 400-ml. beaker over a period of 1 minute with vigorous agitation provided by a mechanically driven paddle stirrer. Sulfur dioxide is evolved while β -isovalerolactam-N-sulfonyl chloride precipitates as a gritty, crystalline, white solid (Note 6). The major portion of dissolved sulfur dioxide is removed by impinging a vigorous stream of air on the surface of the liquid in the beaker until the temperature of the mixture rises again after falling to $0-4^{\circ}$. The precipitate is removed by suction filtration and is washed three times with 33-ml. portions of ice water. The yield of moist product containing 10–20% water is 52–56 g. (Note 7). The product in this form is more suitable for subsequent conversion to the free β -lactam than if it is anhydrous or in a more coarsely crystalline form.

To prepare the anhydrous compound, the solid is dissolved in methylene chloride, whereupon the water separates as the upper phase. The organic layer is dried over anhydrous sodium sulfate, and the solvent is removed under reduced pressure at room temperature to give a colorless, crystalline mass, m.p. $75-77^{\circ}$. Small amounts of the pure compound may be obtained in the form of long needles by recrystallization from ether, m.p. $77-78^{\circ}$. The yield is 43–46 g. (65–70%) in anhydrous form (Note 8).

B. β -Isovalerolactam. A 200-ml. beaker is provided with a combination pH electrode, a mechanically driven paddle stirrer, a thermometer, and a syringe or dropping funnel (Note 9). An amount of water just sufficient for immersion of the pH electrode (20 ml.) is introduced, and with vigorous stirring the first portion

(about one quarter) of the 52–56 g. (about 0.20–0.22 mole) of moist β -isovalerolactam-N-sulfonyl chloride is added. The liberated acid is neutralized by dropwise addition of approximately 10*N* sodium hydroxide solution (Note 10) to maintain the pH of the mixture between 2 and 8, and preferably in the range 5–7 (Note 11). The temperature is kept at 20–25° with cooling supplied by an ice bath as necessary. More lactam-N-sulfonyl chloride is added as the hydrolysis proceeds.

Hydrolysis is very sluggish at first, especially if anhydrous or coarsely crystalline sulfonyl chloride is used. Hydrolysis of the first one quarter to one half of the sulfonyl chloride requires 1–3 hours, and by that time the increasing salt concentration of the solution will cause the separation of the β -lactam as a second liquid phase. The sulfonyl chloride is significantly more soluble in this water-containing lactam phase, and as a result the rate of hydrolysis increases markedly (Note 12). Hydrolysis of the remainder of the sulfonyl chloride can be completed in about 30 minutes to 1 hour. The pH is adjusted finally to 7, and the mixture is cooled to 10° while being repeatedly seeded with sodium sulfate decahydrate. This converts all the precipitated sodium sulfate to the decahydrate (Note 13), and the β -lactam which originally separated in oily form is dissolved. The sodium sulfate decahydrate is removed by suction filtration and is washed with 90 ml. of chloroform. Small portions of the chloroform washings are then used for repeated extraction of the lactam from the salt solution. The extracts are combined, dried over anhydrous potassium carbonate, and distilled through an 8-in. Vigreux column. Most of the chloroform is removed by distillation at atmospheric pressure, and the product is distilled under reduced pressure, b.p. 70° (1.0 mm.), n_D^{25} 1.4475, freezing point 14.7° (Note 14), weight 16.7–17.3 g. (51–53% overall from chloro-sulfonyl isocyanate). The product is 99.8% pure by vapor phase chromatographic analysis.

2. Notes

1. A jacket which is suitable for holding dry ice may be made easily for use with a cylindrical dropping funnel. The neck and

bottom of a narrow-mouthed polyethylene bottle are cut off, and two or three vertical slits are made at the narrow end to allow it to slip over the body of the dropping funnel and rest on the stop-cock barrel. The size of the dropping funnel will determine the size of polyethylene container to be used.

2. The checkers used anhydrous sulfur dioxide supplied in cylinders by the Matheson Co., Inc., East Rutherford, New Jersey, without further purification. Traces of moisture will not interfere with the reaction, and it is sufficient if the liquid sulfur dioxide is clear and colorless. If necessary, however, the gaseous sulfur dioxide may be dried with anhydrous calcium chloride before condensing it.

3. Addition of potassium chloride may be omitted if the chloro-sulfonyl isocyanate is free of sulfur trioxide. Otherwise, traces of sulfur trioxide will give rise to a yellow or brown coloration of the reaction mixture and to formation of small amounts of by-products which, because of their emulsifying activity, may interfere with further processing.

4. The reaction may also be carried out at higher temperatures, *e.g.*, at -10° , with simultaneous addition of gaseous isobutylene over a prolonged period of time. This, however, results in a reaction product of lower purity than is obtained by the present procedure.

5. The reaction is exothermic, and the rate of addition should be controlled to keep the temperature within the limits indicated.

6. The cycloaddition reaction is accompanied by another reaction giving about 30% of 3-methyl-3-butenamide-N-sulfonyl chloride which is readily hydrolyzed during the aqueous work-up. The β -lactam-N-sulfonyl chloride which is the major product of the reaction is relatively stable to hydrolysis under the conditions of its isolation.

7. The product may be stored for several days before its conversion to the free β -lactam in a polyethylene bag placed in a refrigerator or preferably under dry ice in a Dewar flask.

8. The cycloaddition reaction can also be carried out with ether as solvent, especially in small batches.³

9. For hydrolysis of a much larger quantity of material, a four-necked flask may be employed instead of a beaker.

10. Three moles of sodium hydroxide solution is used per mole of sulfonyl chloride. The use of base of known concentration provides a means of following the hydrolysis as well as determining the true amount of product present for calculating the yield in Part A.

11. At high pH (>10–11) saponification of the sulfonyl chloride to the sodium salt of 3-amino-3-methylbutyric acid-N-sulfonic acid will predominate, and at too low a pH (*e.g.*, pH of 0) hydrolysis to 3-hydroxy-3-methylbutyramide will prevail.

12. Care should be taken that the sulfonyl chloride is not added too rapidly, as the increased hydrolysis rate at this point will not permit adequate control of temperature and pH if a large amount of sulfonyl chloride is present. For repeat preparations a portion of the reaction mixture from a preceding batch may be introduced to achieve a more rapid hydrolysis rate sooner in the reaction. For the first preparation there are ways of increasing the initial rate of hydrolysis, or shortening the time interval before the transition from low to higher hydrolysis rate occurs. These are use of sodium sulfate solution instead of pure water, addition of a few tenths of a gram of potassium iodide, or addition of a small amount (1 ml.) of methylene chloride. However, these steps are not necessary if a reasonable amount of patience is exercised.

13. If seeding with sodium sulfate decahydrate is omitted, the unstable heptahydrate may crystallize.

14. The freezing point given was determined by the checkers as the temperature of a solid-melt equilibrium for a sample of 99.8% purity. The submitter reports the melting point at 15.3° after recrystallization from isopropyl ether and redistillation.

3. Methods of Preparation

The only methods reported³ for the preparation of 4,4-dimethyl-2-azetidinone-1-sulfonyl chloride and 4,4-dimethyl-2-azetidinone are those described here.

Conversion of β -lactam-N-sulfonyl chlorides to the free lactams may also be accomplished by means of reducing agents,³ and for β -lactam-N-sulfonyl chlorides which are hydrolytically more

stable than the one in the present example this represents a method to be preferred over pH-controlled hydrolysis.³ The N-sulfonyl chlorides are reduced to N-sulfinic acids which spontaneously decompose to β -lactams and sulfur dioxide. Among the reducing agents which may be used are thiophenol, hydrogen sulfide, zinc dust, iron powder, and iodide ion. Iodide ion need be used only in catalytic amounts, as the liberated iodine is reduced again to iodide ion by the sulfur dioxide split off.

4. Merits of the Preparation

This procedure illustrates a general method for preparing aliphatic and, in certain cases, aromatic β -lactams containing a free NH group and substituted in either the 4 position or in both the 3 and 4 positions of the 2-azetidinone ring. The major by-product of the cycloaddition step is a β,γ -unsaturated carboxamide-N-sulfonyl chloride which, in the case of certain aromatic olefins, may predominate. Reactions of both β -lactam-N-sulfonyl chlorides and the β,γ -unsaturated carboxamide-N-sulfonyl chlorides have been tabulated.³

β -Lactams substituted only in the 3 position cannot be prepared by the present procedure, since the lactam formed has the nitrogen of the chlorosulfonyl isocyanate attached to the more highly substituted carbon atom of the olefinic double bond in Markownikoff fashion. 2-Azetidinones substituted in the 3 position only have been prepared by Grignard reagent-catalyzed cyclizations of esters of appropriately substituted β -amino acids.^{4, 5}

1. Farbwerke Hoechst AG, Frankfurt on the Main, Germany.

2. R. Graf, *Org. Syntheses*, this volume, p. 23.

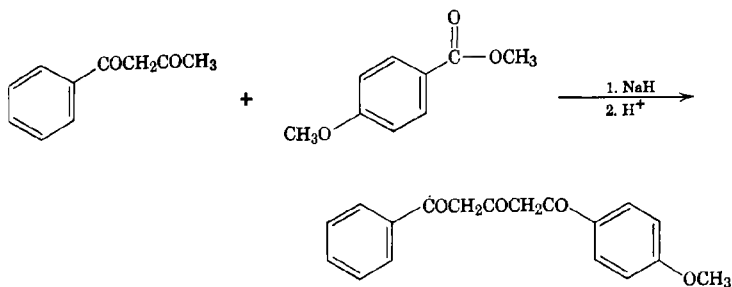
3. R. Graf, *Ann.*, **661**, 111 (1963).

4. R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, **71**, 2129 (1949).

5. G. Cignarella, G. F. Cristiani, and E. Testa, *Ann.*, **661**, 181 (1963); and previous papers in the series.

1-(*p*-METHOXYPHENYL)-5-PHENYL-1,3,5-PENTANETRIONE

[1,3,5-Pentanetrione, 1-(*p*-methoxyphenyl)-5-phenyl-]



Submitted by MARION L. MILES, THOMAS M. HARRIS,
and CHARLES R. HAUSER¹

Checked by VICTOR NELSON, WAYLAND E. NOLAND,
and WILLIAM E. PARHAM

1. Procedure

Caution! Sodium hydride causes severe burns if brought into contact with the skin and, in the dry state, is pyrophoric. Since hydrogen is evolved during the course of the reaction, the necessary precautions against fire and explosion should be taken.

A 1-l. three-necked flask is fitted with a sealed mechanical stirrer, an addition funnel with a pressure-equalizing side arm, and a reflux condenser with a gas take-off at the upper end. The gas take-off is connected by means of rubber tubing to one arm of a glass Y-tube. The other arm of the Y-tube is connected to a source of dry nitrogen gas. The bottom of the Y-tube is immersed just beneath the surface of a little 1,2-dimethoxyethane (monoglyme) contained in a small beaker.

The flask is swept with a stream of dry nitrogen. Monoglyme (100 ml.) (Note 1) and sodium hydride (6 g., 0.25 mole) (Note 2) are placed in the flask. A solution of 8.1 g. (0.050 mole) of

benzoylacetone (Note 3) and 12.5 g. (0.075 mole) of methyl anisate (Note 4) in 100 ml. of monoglyme is placed in the addition funnel. The funnel is stoppered, and the nitrogen flow rate is adjusted so that approximately 10 bubbles per minute are emitted from the bottom of the Y-tube. The sodium hydride slurry is stirred and heated on the steam bath. When reflux is obtained, the solution of benzoylacetone and methyl anisate is added slowly so that hydrogen evolution is maintained at a controllable rate. The reaction mixture is kept at the reflux temperature for 6 hours.

The reaction mixture is then cooled to room temperature, the reflux condenser is replaced with a distillation condenser equipped with a vacuum take-off, and most of the solvent is removed under reduced pressure (*ca.* 100 mm.) until a thick paste is obtained. The mixture is then cooled in an ice water bath, and 150 ml. of ether is added. Cold water (200 ml.) is placed in the addition funnel, and initially the water is added dropwise (*Caution! Vigorous evolution of hydrogen*) until the excess sodium hydride is destroyed; then the remainder of the water is added more rapidly (Note 5).

The reaction mixture is poured into a 1-l. separatory funnel, and the aqueous layer is removed. The ether layer is extracted with two 100-ml. portions of water and then with 100 ml. of aqueous 1% sodium hydroxide. The extracts are combined with the original aqueous layer, and the resulting solution is washed once with 100 ml. of fresh ether. Crushed ice (100 g.) is added to the solution, followed by 30 ml. of 12*N* hydrochloric acid. The product, which precipitates at this point, is removed by filtration, washed with water, and recrystallized from 450 ml. (Note 6) of 95% ethanol. The yield of 1-(*p*-methoxyphenyl)-5-phenyl-1,3,5-pentanetrione is 11.4–12.8 g. (77–86%) (Note 7), m.p. 120–121.5°.

2. Notes

1. Eastman Kodak (Eastman grade) 1,2-dimethoxyethane was dried for 24 hours over calcium hydride, distilled from sodium metal, and then stored over calcium hydride.

2. The submitters used sodium hydride obtained as a 50% dispersion in mineral oil from Ventron Corp. This material was used as received.

3. The benzoylacetone was obtained from Eastman Kodak (Eastman grade), m.p. 57–58°.

4. Eastman Kodak (Eastman grade) methyl anisate was used without further purification.

5. The checkers observed that the thick brown oil, which separates as the water is added, may partially solidify when stored overnight. The solid was melted on a steam bath, placed in the separatory funnel, and processed with the rest of the reaction mixture as described.

6. The checkers used 480 ml. of 95% ethanol.

7. The checkers found that the product retained as much as 2 g. of ethanol after 20 minutes of air drying. The product was dried to constant weight.

3. Methods of Preparation

The method described is that of Miles, Harris, and Hauser² and is an improvement over the earlier procedure of Hauser and co-workers.^{3, 4} In the earlier method the dianion of benzoylacetone, formed by the action of alkali amide in liquid ammonia, was treated with methyl anisate to yield 1-(*p*-methoxyphenyl)-5-phenyl-1,3,5-pentanetrione (61% based on the ester). This compound has also been prepared by the base-catalyzed ring opening of 2-(*p*-methoxyphenyl)-6-phenyl-4-pyrone; however, no yield is reported.⁵

4. Merits of the Preparation

This procedure appears to be fairly general for the aroylation of β -diketones to give 1,3,5-triketones. Using this method, the submitters² have aroylated benzoylacetone with methyl benzoate (87%), methyl *p*-chlorobenzoate (78%), and ethyl nicotinate (69%). Also, acetylacetone has been monobenzoylated with methyl benzoate to form 1-phenyl-1,3,5-hexanetrione in 75% yield or dibenzoylated with the same ester to form 1,7-diphenyl-

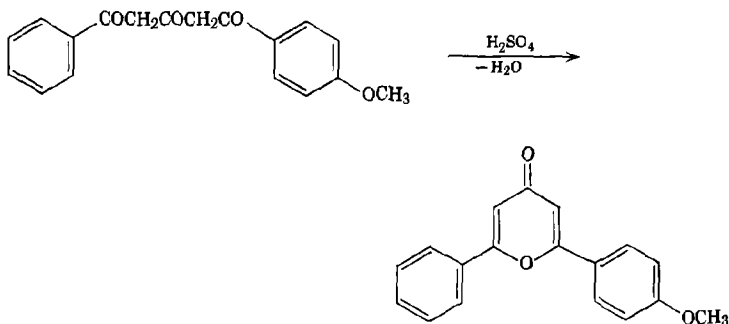
1,3,5,7-heptanetetraone in 56% yield.⁶ Symmetrical 1,5-diaryl-1,3,5-pentanetriones can be conveniently prepared by a similar procedure² from acetone and two equivalents of the appropriate aromatic ester; for example, 1,5-diphenyl-1,3,5-pentanetrione and 1,5-di(*p*-methoxyphenyl)-1,3,5-pentanetrione are formed in yields of 82% and 77%, respectively.

1,3,5-Triketones are useful intermediates in the preparation of 4-pyrones, 4-pyridones,^{3, 4} and other cyclic products.

1. Chemistry Department, Duke University, Durham, North Carolina. This research was supported by the National Science Foundation.
2. M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 1007 (1965).
3. C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).
4. R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).
5. G. Soliman and I. E. El-Kholy, *J. Chem. Soc.*, 1755 (1954).
6. M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 3884 (1963).

2-(*p*-METHOXYPHENYL)-6-PHENYL-4-PYRONE

[4H-Pyran-4-one, 2-(*p*-methoxyphenyl)-6-phenyl-]



Submitted by MARION L. MILES and CHARLES R. HAUSER¹
 Checked by VICTOR NELSON, WAYLAND E. NOLAND,
 and WILLIAM E. PARHAM

1. Procedure

In a 50-ml. Erlenmeyer flask is placed 10 ml. of concentrated (36*N*) sulfuric acid (Note 1), and the flask is then immersed in

an ice water bath. When the temperature of the acid reaches 0°, 2.96 g. (0.010 mole) of 1-(*p*-methoxyphenyl)-5-phenyl-1,3,5-pentanetrione (Note 2) is added in small portions. As each portion is added, the flask is swirled until the triketone dissolves. After the addition is completed, the solution is kept at 0° for 1 hour and then poured into 500 ml. of cold water. To the resulting slurry is added solid sodium bicarbonate until a pH of 7-8 (Note 3) is obtained. The mixture is filtered, and the filter cake is washed with cold water and then recrystallized from 15 ml. of 95% ethanol to give 2.46-2.72 g. (88-98%) of 2-(*p*-methoxyphenyl)-6-phenyl-4-pyrone, m.p. 161-163°.

2. Notes

1. Regular commercial grade of concentrated sulfuric acid (sp. gr. 1.84) obtained from the General Chemical Division of Allied Chemical Corporation was used.

2. For the preparation of this compound see *Org. Syntheses*, this volume, p. 57.

3. This pyrone has a tendency to form a salt in aqueous sulfuric acid. The submitters used "Hydrion" paper to check the pH.

3. Methods of Preparation

The method is an adaptation of the procedure of Light and Hauser.² 2-(*p*-Methoxyphenyl)-6-phenyl-4-pyrone has been prepared in 50% yield by a Claisen-type acylation of *p*-methoxyacetophenone with ethyl phenylpropiolate accompanied by cyclization.³

4. Merits of the Preparation

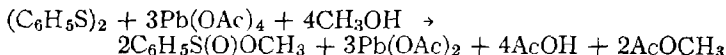
This procedure offers an extremely simple and fairly general method for the preparation of 2,6-disubstituted 4-pyrones. Pyrones which have been prepared² by this procedure are: 2-methyl-6-phenyl-4-pyrone (60%), 2-(*p*-chlorophenyl)-6-methyl-4-pyrone (90%), 2,6-diphenyl-4-pyrone (91%), 2-(*p*-chlorophenyl)-6-phenyl-4-pyrone (90%), 2-phenyl-6-(3-pyridyl)-4-py-

rone (91%), 5,6,7,8-tetrahydroflavone (76%), 4'-methoxy-5,6,7,8-tetrahydroflavone (70%), cyclopenteno[*b*]-6-(*p*-methoxyphenyl)-4-pyrone (59%), and flavone (63%).

1. Chemistry Department, Duke University, Durham, North Carolina. This research was supported by the National Institutes of Health.
2. R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).
3. G. Soliman and I. E. El-Kholy, *J. Chem. Soc.*, 1755 (1954).

METHYL BENZENESULFINATE

(Benzenesulfinic acid, methyl ester)



Submitted by LAMAR FIELD¹ and J. MICHAEL LOCKE²

Checked by JOHN J. MILLER and WILLIAM D. EMMONS

1. Procedure

Caution! Care should be taken to keep methyl benzenesulfinate off the skin (Note 1).

In a 5-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer and a reflux condenser carrying a drying tube are placed 54.6 g. (0.25 mole) of diphenyl disulfide (Note 2), 450 ml. of chloroform (Note 3), and 450 ml. of methanol. To the stirred solution at the reflux temperature is added 443.4 g. (1.00 mole) of lead tetraacetate (Note 4) in 2 l. of chloroform during 8 hours. Owing to formation of lead dioxide, the initially yellow solution becomes dark brown during the addition. The mixture is kept at the reflux temperature overnight (about 12 hours), after which 2 l. of chloroform is removed by distillation at atmospheric pressure (Note 5). The mixture then is cooled to room temperature, and 330 ml. of distilled water is added with stirring to decompose any excess lead tetraacetate. Lead dioxide is removed by filtration of the entire mixture using a Celite®-coated filter paper. The chloroform layer is washed with distilled water until the washings are free of lead ions (Note 6.) The chloroform solution is dried over anhydrous magnesium

sulfate and, after separation of the drying agent, is concentrated by means of a rotating-flask evaporator. The oily yellow residue is left overnight under vacuum (about 0.1 mm.) to remove any traces of hexachloroethane (Note 7). Distillation is effected through a 15-cm. Vigreux column under reduced pressure (Note 8). The yield of methyl benzenesulfinate is 48.6–53 g. (62–68%), b.p. 59–60° (0.04 mm.), 76–78° (0.45 mm.); n_D^{25} 1.5410–1.5428, reported n_D^{20} 1.5400,³ 1.5440.⁴

2. Notes

1. The checkers experienced an extreme and prolonged burning sensation on contact.

2. Diphenyl disulfide, supplied by Distillation Products Industries, Rochester 3, New York, was used as received.

3. Reagent grade chloroform is satisfactory.

4. Used as received from Arapahoe Chemicals, Inc., Boulder, Colorado. This product, usually about 85–96% lead tetraacetate moist with acetic acid, is stored at about 5°. The molar amount specified is based on occasional iodometric titration (Arapahoe brochure) as follows:⁵ An accurately weighed sample of about 0.5 g. is dissolved in 5 ml. of glacial acetic acid with gentle warming, and 100 ml. of an aqueous solution of 12 g. of anhydrous sodium acetate and 1 g. of potassium iodide is added. After several minutes, with occasional swirling, the flask wall is rinsed with water. Liberated iodine is titrated with 0.1*N* sodium thiosulfate to a starch end point. The percent of lead tetraacetate is calculated from the formula 22.17 (milliliters of thiosulfate) (normality of thiosulfate)/(weight of sample).

The submitters recommend that the lead tetraacetate be added in eight separate portions of 0.125 mole of lead tetraacetate, each in 250 ml. of chloroform, because the solution of lead tetraacetate decomposes on standing.

5. This can be done conveniently by removing the reflux condenser and replacing it with apparatus for downward distillation.

6. A solution of sodium sulfide can be used to test for the presence of lead ions in the wash liquors. The checkers found

that the yield can be improved somewhat by extraction of the initial water layer with chloroform.

7. The small amount of hexachloroethane produced during the reaction presumably is formed from chloroform by a free radical process.

8. The residue after distillation is diphenyl disulfide. It may be recovered by recrystallization from ethanol. The methyl benzenesulfinate may be pale yellow when first distilled, but if so it becomes colorless on standing. If possible, a spinning-band column should be used for distillation, and distillation should be as rapid as possible; use of a 47-cm. spinning-band column gave analytically pure ester, n_D^{25} 1.5436 (cf. Field and co-workers).⁶

3. Methods of Preparation

Methyl benzenesulfinate has been prepared by the three-stage process of reduction of benzenesulfonyl chloride to benzenesulfinic acid, conversion of the acid to benzenesulfinyl chloride, and esterification of the chloride with methanol.^{3, 7} It has been prepared also by ozonolysis of methyl benzenesulfonate.⁴ The present procedure is based on one reported by Field, Hoelzel, and Locke.⁶

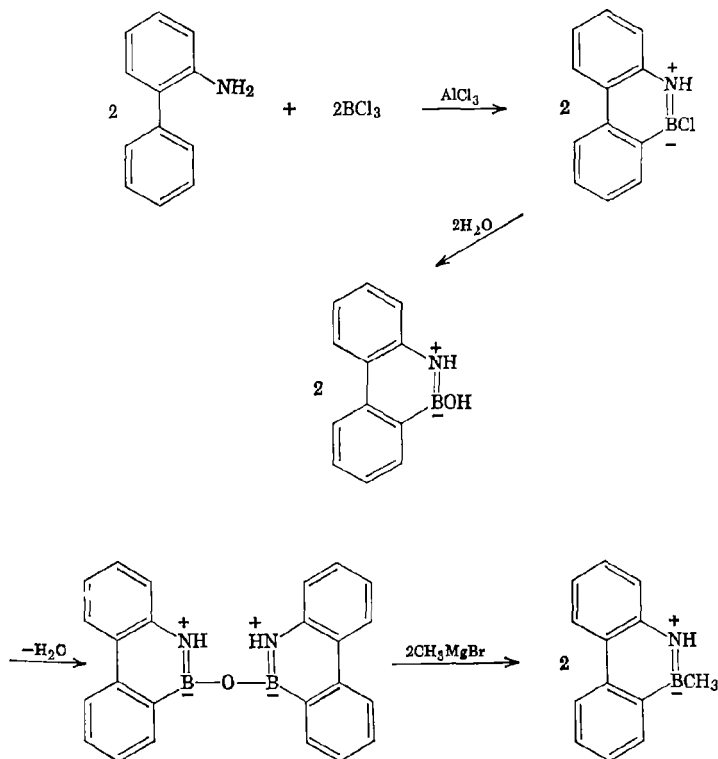
4. Merits of the Preparation

This procedure affords a one-step synthesis of aromatic sulfinic esters from readily available starting materials. It is successful with a variety of types of aromatic sulfinic esters.⁶ The method is rather unattractive for aliphatic disulfides, however, because the nature of by-products formed makes rigorous purification of the sulfinic esters impracticable.⁸

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2. Department of Chemistry, University of Southampton, Southampton, England.
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10-METHYL-10,9-BORAZAROPHENANTHRENE
(Dibenz[*c,e*][1,2]azaborine, 5,6-dihydro-6-methyl-)



Submitted by M. J. S. DEWAR, R. B. K. DEWAR, and Z. L. F. GAIBEL¹
 Checked by JACK A. SNYDER and B. C. MCKUSICK

1. Procedure

A. *Bis(10,9-borazarophenanthryl) ether*. *Caution! All the operations involving boron trichloride should be carried out in a good hood.*

A solution of 250 g. (1.48 moles) of 2-aminobiphenyl (Note 1) in 2.0 l. of dry xylene (Note 2) is placed in a 5-l. four-necked flask equipped with a 500-ml. pressure-equalized dropping funnel, a reflux condenser fitted with a drying tube loosely packed with calcium chloride, a thermometer, and a mechanical stirrer. A solution of 250 g. (174 ml., 2.14 moles) of boron trichloride in 250 ml. of very cold xylene is placed in the dropping funnel (Note 3).

The boron trichloride solution is added dropwise to the stirred amine solution over a period of 30 minutes; a thick precipitate forms as the first third of the solution is added, but it gradually dissolves, and the reaction mixture is a clear, dark amber solution at the end of the addition. The mixture is heated under reflux for 1 hour; the temperature of the mixture gradually rises from 110° to 140° as hydrogen chloride and boron chloride are evolved (Note 4). The mixture is cooled to about 100°, the dropping funnel is replaced by a powder funnel, and 15 g. of anhydrous aluminum chloride is cautiously added. The funnel is replaced by a well-greased stopper (Note 5), and the mixture is heated under reflux for 2 hours. The mixture is cooled slightly, and an additional 5 g. of aluminum chloride is added. The reaction mixture is heated under reflux at least 16 hours, and then the reflux condenser is replaced by a Claisen head leading to a water condenser and receiver. About 80% of the solvent (1.6–1.7 l.) is distilled with vigorous stirring.

A dropping funnel with a pressure-equalizing arm is inserted in place of the stopper, and 2.5 l. of distilled water is added from it with vigorous stirring. The reaction with water is extremely exothermic at first, and the first 30 ml. of water is added not faster than 1 drop per second. The mixture is steam-distilled with heating and vigorous stirring until the head temperature reaches 100°. A fresh receiver is attached, and the distillation is continued until the distillate no longer smells of xylene; this is usually after about 300 ml. of distillate has been collected in the receiving vessel (Note 6). If necessary, water is added from time to time to maintain the liquid level in the flask. The flask is cooled to room temperature with vigorous stirring (Note 7), and crystalline 10-hydroxy-10,9-borazarophenanthrene separates.

The solid is collected by suction filtration, washed with about 750 ml. of water, and dried overnight at 75–80° in an oven under reduced pressure (200 mm. or below). Dehydration to bis(10,9-borazarophenanthryl) ether usually takes place during the drying. The ether, a tan solid, weighs 221–250 g. (80–91%) (Note 8).

B. 10-Methyl-10,9-borazarophenanthrene. The tan bis(10,9-borazarophenanthryl) ether from the previous step is transferred to a dry, 5-l., four-necked flask equipped with a mechanical stirrer, a nitrogen inlet, a 1-l. pressure-equalized dropping funnel, a thermometer, and a very efficient reflux condenser with a drying tube packed with silica gel at the top (Note 9). A 3.2-l. portion of anhydrous ether is placed in the flask, and the mechanical stirrer is started. The flask is cooled in an ice bath, and 700 ml. (2.1 moles) of 3*M* methylmagnesium bromide solution in ether (Note 10) is added dropwise through the funnel during 1 hour. The reaction mixture is heated under reflux overnight. The mixture is cautiously and slowly poured into 1 l. of ice water and then cautiously acidified with 385 ml. (10% excess) of 6*N* hydrochloric acid. The ether layer is separated, and the water layer is extracted with five 400-ml. portions of ether. The combined ether fractions are washed with 200 ml. of saturated sodium bicarbonate solution; the sodium bicarbonate solution is washed with 300 ml. of ether, which is added to the other ether fractions.

The combined ether fractions are dried over 50 g. of magnesium sulfate, the ether is removed at reduced pressure, and the residue is dried overnight at 60° (10 mm.). The resulting slightly oily, crystalline, brown solid is a mixture of 10-methyl-10,9-borazarophenanthrene, bis(10,9-borazarophenanthryl) ether, and tars; weight about 220 g.; m.p. 92–98°. The methyl derivative is isolated by continuous chromatography over about 500 g. of Merck basic alumina (chromatography grade) in the apparatus shown in Fig. 1 (Note 11). The crude product is placed on top of the alumina, 4 l. of petroleum ether (b.p. 30–60°) is poured into the flask, and the extractor is operated for 30–35 hours. 10-Methyl-10,9-borazarophenanthrene gradually crystallizes as fine needles on the walls of the flask.

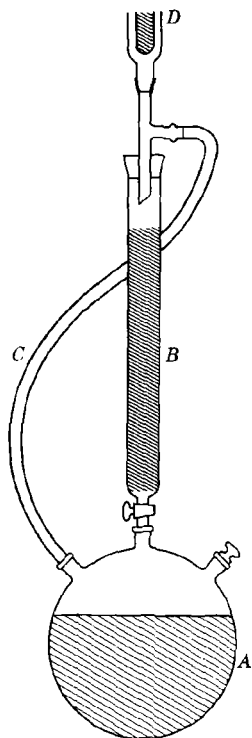


FIG. 1. *A*, 5-l. three-necked flask with electric heating mantle; *B*, alumina column 45 cm. $\times$ 3.8 cm. (Merck basic alumina); *C*, polyethylene tubing; *D*, condenser (see Note 11).

The flask is cooled to room temperature, all solvents are allowed to drain from the column, and 120–150 g. of colorless product, m.p. 99–101°, is separated by filtration and washed with petroleum ether. A second crop, weight 25–40 g., m.p. 98.5–101.0°, is obtained by concentrating the combined filtrates to about 250 ml. and cooling the concentrate to room temperature. The crops of 10-methyl-10,9-borazarophenanthrene are combined; weight 155–182 g. (54–65% based on 2-aminobiphenyl). The product is sufficiently pure for many purposes. A purer product, m.p. 103–104°,² may be obtained by recrystallization from petroleum ether (b.p. 35°) (Note 12).

2. Notes

1. A technical grade of 2-aminobiphenyl obtainable from Columbia Organic Chemicals Co. is satisfactory. This black material contains the carcinogenic 4-isomer; it should therefore be handled carefully to avoid contact with the skin. Purification of the amine by vacuum distillation removes the black impurities but does not improve either the yield or the quality of the final product.

2. The xylene is dried over sodium wire or sodium-lead alloy before use.

3. Boron trichloride boils at 13°. To prepare the solution, the submitters poured liquid boron trichloride into a tared beaker containing dry xylene until the weight increased by 250 g. The beaker was in a methanol-ice bath.

The checkers placed 250 ml. of dry xylene in a 500-ml. round-bottomed flask marked with a line corresponding to a volume of 424 ml. and with a gas inlet above the line. A cold finger containing a mixture of dry ice and methanol was attached to the flask, which was immersed in the same mixture. Gaseous boron trichloride (Matheson Co.) was passed in until the flask was filled to the 424-ml. line, and the cold solution was transferred to the dropping funnel.

4. During the most vigorous evolution of gas it is advisable to replace the drying tube by a tube leading to the back of the hood or to a gas absorption trap.

5. Unless the stopper is well greased, the aluminum chloride will cement it to the flask.

6. The purpose of the steam distillation is to remove all the xylene. If the crystals are collected prematurely, the last traces of xylene are hard to remove.

7. If the mixture is not vigorously stirred while cooling, an intractable cake forms at the bottom of the flask.

8. The product may be bis(10,9-borazarophenanthryl) ether, 10-hydroxy-10,9-borazarophenanthrene, or a mixture. The melting point of either product varies widely with the method of determination. The checkers placed analytical samples in a bath at 125° with the temperature rising 9–12° per minute and

observed m.p. 154–159° for the ether, m.p. 133° (with frothing) for the hydroxy compound. The infrared spectrum of the hydroxy compound has a band at $2.83\ \mu$ that is lacking in the spectrum of the ether. According to the submitters, either the ether or the hydroxy compound can be used in step B. The checkers used only the ether.

The tan product is almost pure. Extraction with petroleum ether (b.p. 60–70°) in a Soxhlet gives white crystals.

9. A West condenser and a Friedrich condenser in tandem are recommended.

10. The methylmagnesium bromide solution is obtainable from Arapahoe Chemicals, Inc., Boulder, Colorado.

11. This procedure may prove useful in other cases where impurities are strongly adsorbed on alumina, it avoids the use of enormous volumes of solvent. The heating mantle is controlled by a Variac, set so that the liquid level remains constant. The plastic tubing should not be of Tygon[®], since this is attacked by the solvent, polyethylene tubing is suitable. An efficient condenser is essential, the use of a West condenser and a Friedrich condenser in tandem is recommended. A similar but more complicated apparatus is described by Meier and Fletschinger.³

12. Some unreacted bis(10,9-borazarophenanthryl) ether can be recovered from the column by extraction with methanol.

3. Methods of Preparation

10-Chloro-10,9-borazarophenanthrene has been obtained only by Friedel-Crafts cyclization of the adduct from 2-aminobiphenyl and boron trichloride;² the procedure described here is an improvement on the original process,² in which no solvent was used.

10-Methyl-10,9-borazarophenanthrene has been obtained by the action of methylmagnesium halides on 10-chloro-10,9-borazarophenanthrene² or bis(10,9-borazarophenanthryl) ether.⁴ The former preparation was satisfactory when pure 2-aminobiphenyl was available, but existing grades lead to products containing intractable impurities, presumably derived from the 4-isomer. These impurities are eliminated during the hydrolysis to 10-hydroxy-10,9-borazarophenanthrene.

4. Merits of the Preparation

10,9-Borazarophenanthrene was the first representative of a new class of heteroaromatic compounds containing boron atoms in six-membered aromatic rings.¹ These compounds are of a different order of stability from previously known types of organoboron compounds, being chemically similar to "normal" aromatics, and their discovery has opened up a new field of aromatic chemistry. The procedure indicated here has been used to prepare a large number of related aromatic systems.

The cyclization can be carried out with halogenated amines, and substitution products of the new ring systems can also be obtained in the conventional way, by nitration, etc. Similar compounds can be prepared directly by using arylboron dichlorides in place of boron trichloride in the procedure indicated above. The parent borazarene derivatives, with hydrogen attached to boron, can be made from the B-hydroxy compounds with lithium aluminum hydride in the presence of aluminum chloride.^{4, 5} N-Alkyl derivatives can be made either by using N-alkyl derivatives of the aminobiphenyls as starting materials, or by N-alkylation of the unsubstituted compounds via their N-lithio derivatives.⁵ Apart from their inherent interest, compounds of this type can serve as intermediates in various syntheses. Thus benzocinnolines and 2,2'-dihydroxybiphenyls can be obtained from derivatives of 2-aminobiphenyl.^{5, 7}

¹ Department of Chemistry, The University of Texas, Austin, Texas

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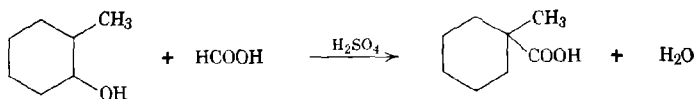
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1-METHYLCYCLOHEXANECARBOXYLIC ACID

(Cyclohexanecarboxylic acid, 1-methyl-)



Submitted by W. HAAFF¹

Checked by D. M. GALE and B. C. MCKUSICK

1. Procedure

Caution! Because carbon monoxide is evolved, the reaction should be carried out in a good hood.

Two hundred seventy milliliters (497 g., 4.86 moles) of 96% sulfuric acid (Note 1) is poured into a 1-l. three-necked flask equipped with a paddle stirrer driven by a powerful motor, a dropping funnel with a gas by-pass, and a thermometer that dips into the acid. The reaction mixture is stirred *vigorously* (Note 2) and maintained at 15–20° by means of a cooling bath as 3 ml. of 98–100% formic acid (Note 3) is added dropwise. Under the same conditions, a solution of 28.5 g. (0.25 mole) of 2-methylcyclohexanol (Note 4) in 46 g. (1.00 mole) of 98–100% formic acid is added in the course of 1 hour. The reaction mixture foams during the additions. The mixture, which is a very light cream color, is stirred for 1 hour at 15–20° and then is poured with stirring onto 1 kg. of crushed ice in a 4-l. beaker. The carboxylic acid separates as a white solid.

The acid is taken up in 200 ml. of hexane (Note 5), the hexane layer is separated, and the aqueous layer is extracted with two 150-ml. portions of hexane. The combined hexane solutions are extracted twice with a mixture of 175 ml. of 1.4*N* potassium hydroxide solution and 50 g. of crushed ice. The two alkaline solutions are combined and extracted with 100 ml. of hexane to remove traces of neutral oil, and then acidified to pH 2 with 12*N* hydrochloric acid (about 35 ml.). The liberated carboxylic acid is taken up in 150 ml. of hexane. The aqueous layer is extracted

with 100 ml. of hexane, and the combined hexane layers are washed with 75 ml. of water and dried over 3 g. of anhydrous magnesium sulfate. The hexane is evaporated by warming the solution at 30–60° (15–30 mm.) overnight. The residue is 33–36 g. (93–101%) of colorless 1-methylcyclohexanecarboxylic acid, m.p. 34–36°, that is pure enough for most purposes. Distillation from a 100-ml. Claisen flask (Note 6) gives 31.5–33.5 g. (89–94%) of the acid, b.p. 132–140° (19 mm.), 79–81° (0.5 mm.); m.p. 38–39°.

2. Notes

1. Three moles of 99–100% sulfuric acid may be used in place of the 96% sulfuric acid.

2. With slow stirring there is a higher concentration of carbon monoxide and hence less rearrangement. For example, cyclohexanol in a slowly stirred reaction mixture gave 75% cyclohexanecarboxylic acid and 14% 1-methylcyclopentanecarboxylic acid; with rapid stirring the corresponding yields were 8% and 61%.²

3. Technical grade 85% formic acid can be substituted for 98–100% formic acid if the decrease in sulfuric acid concentration that would result is compensated for by a suitable increase in the amount of sulfuric acid charged.

4. The checkers used “*o*-Methylcyclohexanol,” available from K & K Laboratories, Jamaica, New York. They redistilled it before use; b.p. 70–80° (20 mm.), n_D^{25} 1.4617. 3- or 4-Methylcyclohexanol can be used in place of 2-methylcyclohexanol, or mixtures of the three can be used.

5. Normal hexane, commercial grade, from the Phillips Petroleum Co., Bartlesville, Oklahoma, was used. Other organic solvents, such as benzene, are satisfactory.

6. The checkers used a 30-cm. spinning-band column for the distillation.

3. Methods of Preparation

1-Methylcyclohexanecarboxylic acid can be prepared by carbonylation of the Grignard reagent from 1-chloro-1-methylcyclohexane³ or by Friedel-Crafts condensation of 1-chloro-1-methylcyclohexane with methyl 2-furancarboxylate followed by saponi-

fication and oxidation ⁴ It can also be prepared by successive hydrogenation and saponification of the Diels-Alder adduct from butadiene and methyl methacrylate,⁵ by oxidation of 1-methyl-1-acetylcyclohexane with nitric acid ⁶ or sodium hypobromite,⁷ and by the present method of synthesis ⁸

4. Merits of the Preparation

Carboxylation by formic acid is a rapid and simple method of preparing many tertiary carboxylic acids ⁸ It can be applied to primary, secondary, and tertiary alcohols as well as to olefins and other compounds equivalent to the alcohols under the reaction conditions The reaction often proceeds with rearrangement of the carbon skeleton. The scope of the reaction is indicated by Table I, which lists 13 alcohols to which the reaction has been applied

TABLE I
CARBOXYLATION OF ALCOHOLS TO ACIDS

Alcohol		Acids Formed ^a	Yield of RCO ₂ H, % ^b
1- or 2-Butanol	100	2 Methylbutyric acid	36 or 43
<i>t</i> -Butyl alcohol	95	Trimethylacetic acid	75
1- or 2-Pentanol	80	2,2 Dimethylbutyric acid	76 or 81
	20	C ₁₁ acids	
2-Methyl-2-butanol	10	Trimethylacetic acid	73
	42	2,2-Dimethylbutyric acid	
	12	C ₇ acids	
	36	C ₁₁ acids	
2,2,3-Trimethyl-2-butanol	100	2,2,3,3-Tetramethylbutyric acid	88
2,2-Dimethyl-1-propanol	100	2,2-Dimethylbutyric acid	83
Cyclopentanol	63	Cyclopentanecarboxylic acid	26
	37	<i>cis</i> -9-Decalin carboxylic acid	
Cyclohexanol	80	1-Methylcyclopentanecarboxylic acid	78
	9	Cyclohexanecarboxylic acid	
	11	C ₁₃ acids	
Cycloheptanol	100	1 Methylcyclohexanecarboxylic acid	91
2-Decalol	80	<i>cis</i> -9-Decalin carboxylic acid	95
	20	<i>trans</i> -9-Decalin carboxylic acid	
1-Hydroxyadamantane	100	1-Adamantanecarboxylic acid ^{10 11}	95

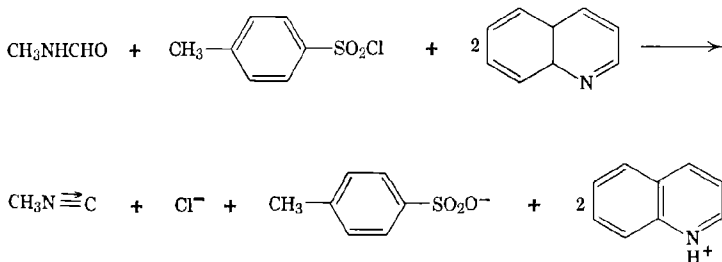
^aThe number before each acid is its volume percent in the mixture carboxylic acids formed

^bTotal yield of all carboxylic acids formed

In a related reaction, saturated hydrocarbons with a tertiary hydrogen are carboxylated by a mixture of formic acid, *t*-butyl alcohol, and sulfuric acid.^{9, 10}

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METHYL ISOCYANIDE



Submitted by R E SCHUSTER, JAMES E SCOTT
and JOSEPH CASANOVA, JR.¹

Checked by JOHN A DUPONT and WILLIAM D EMMONS

1. Procedure

Caution! Methyl isocyanide should be prepared in a good hood since it is toxic and has a very unpleasant odor. The reaction and subsequent distillation of the product should be conducted behind safety shields (Note 1).

In a 2-l. four-necked flask (Note 2) equipped with a 250-ml. pressure-equalizing dropping funnel, a sealed mechanical stirrer, a thermometer, and a receiver trap (Note 3) are placed 1034 g. (8.0 moles) of quinoline and 572 g. (3.0 moles) of *p*-toluenesulfonyl

chloride (Note 4). The solution is heated to 75° by an oil bath and the system evacuated to a pressure of 15 mm. The receiver is cooled in a bath of liquid nitrogen (Note 5). While the solution is vigorously stirred and maintained at this temperature, 118 g. (2.0 moles) of N-methylformamide (Note 4) is added dropwise to maintain a smooth distillation rate. The addition is complete in 45–60 minutes.

The material which collects in the receiver is distilled through a 15-cm. Vigreux column at atmospheric pressure. Methyl isocyanide, a colorless, vile-smelling liquid, is collected at 59–60°; weight 57–61 g. (69–74%) (Note 6). Analysis by gas liquid chromatography indicates that the purity exceeds 99% (Note 7).

2. Notes

1. An explosion involving ethyl isocyanide has been reported.² For this reason, prudence dictates the use of adequate shielding in all heating operations.

2. A three-necked flask may be used by employing a suitable adapter on one of the necks. The checkers used a standard wide-bore, 75-degree side-arm adapter fitted with a long-stemmed thermometer extending into the reaction solution. A Trubore[®] stirrer equipped with a semicircular Teflon[®] paddle was also used.

3. A vapor trap having a wide-bore inlet tube and the appropriate condensate capacity is used. The checkers used a 4.8 cm. x 30.0 cm. trap having a 2.0 cm. x 18.0 cm. inlet tube. Best results are obtained when the trap is connected directly to the flask or the adapter (see Note 2) by a wide-bore tube. Ground-glass joints should be used throughout the apparatus.

4. All materials were obtained from Eastman Kodak Company. Quinoline, practical grade, b.p. 72–74° (0.2 mm.), was freshly distilled from zinc dust. If undistilled quinoline is employed, a major contaminant, which appears to be methyl isocyanate, will be formed. "White label" *p*-toluenesulfonyl chloride and N-methylformamide were used without further purification.

5. The checkers found that a bath of dry ice and acetone worked equally well.

6. A single transfer under high vacuum afforded a product of

identical purity. The major contaminants appear to be small amounts of high-boiling starting materials.

7. When a 2-m. polypropylene glycol on firebrick column at 75° is used, the retention volume of methyl isocyanide is 55 cc. of helium. Because of an unknown factor in conditioning the column, it is advisable to perform at least two consecutive analyses.

The checkers employed a 5-ft. 20% Carbowax 20 M (terminated with terephthalic acid) on Chromosorb W (acid washed) column at 60°. Methyl isocyanide showed a retention volume of 300 cc. of helium. Only traces of lower-boiling impurities were observed.

3. Methods of Preparation

Methyl isocyanide has been prepared chiefly by minor modifications of the original method of Gautier,³ which is the alkylation of silver cyanide by an alkyl halide.

4. Merits of the Preparation

The excellent procedures for dehydration of N-alkyl- and N-arylformamides developed by Hertler and Corey⁴ and by Ugi and co-workers⁵ are unsuccessful with low-molecular-weight isocyanides. This common failure is probably due to poor efficiency in extraction of these very polar substances from water. The present method also has been successfully employed for the preparation of smaller quantities of methyl (50%), ethyl (45%), s-butyl (35%) and cyclobutyl (24%) isocyanides.⁶ The procedure is less laborious than that reported earlier for ethyl isocyanide.⁷

1 Department of Chemistry, California State College at Los Angeles, Los Angeles, California

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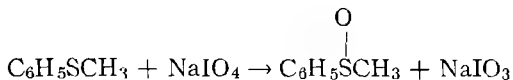
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METHYL PHENYL SULFOXIDE

Submitted by CARL R JOHNSON and JEFFREY E KEISER¹

Checked by WAYLAND E NOLAND, LEONARD J CZUBA,
and WILLIAM E PARHAM

1. Procedure

In a 500 ml round-bottomed flask equipped with a magnetic stirrer are placed 22.5 g (0.105 mole) of powdered sodium metaperiodate and 210 ml of water. The mixture is stirred and cooled in an ice bath (Note 1), and 12.4 g (0.100 mole) of thioanisole (Note 2) is added. The reaction mixture is stirred for 15 hours at ice-bath temperature and is then filtered through a Buchner funnel. The filter cake of sodium iodate is washed with three 30-ml portions of methylene chloride. The water-methylene chloride filtrate is transferred to a separatory funnel, the lower methylene chloride layer is removed, and the water layer is extracted with three 100-ml portions of methylene chloride. The combined methylene chloride extracts are treated with activated carbon (Note 3) and dried over anhydrous sodium sulfate (Note 4). The solvent is removed at reduced pressure to yield 13.6–13.9 g of a slightly yellow oil (Note 5) which crystallizes on cooling. The crude sulfoxide is transferred to a 25 ml distillation flask with the aid of a small amount of methylene chloride. After removal of the solvent, a pinch of activated carbon is added to the distillation flask (Note 6). Simple vacuum distillation (Note 7) of the crude product through a short path still affords 12.7–12.8 g (91%) of pure methyl phenyl sulfoxide, b.p. 78–79° (0.1 mm), m.p. 33–34° (Notes 8 and 9).

2. Notes

1. An insulated ice bucket such as the "Nicer" available from B. F. Goodrich Company is a convenient reservoir for maintaining

an ice bath for long periods of time. The magnetic stirrer operates efficiently through it.

2 Thioanisole (methyl phenyl sulfide) supplied by Aldrich Chemical Company, Milwaukee, Wisconsin, was used without further purification.

3 The checkers used 1 g. of activated carbon.

4 The checkers used 3–5 g. of sodium sulfate.

5 Gas-phase chromatography shows this crude material to be sulfide-free sulfoxide containing a small amount of methylene chloride.

6 The simple technique of adding a pinch of activated carbon to the distillation pot affords a more nearly colorless distillate.

7 No fore run is observed other than a small amount of methylene chloride which does not condense. The pot is taken nearly to dryness.

8 Methyl phenyl sulfoxide is extremely hygroscopic. The melting point is best taken by rapid transfer of the easily super-cooled oil to a melting-point capillary by means of a finely drawn pipet. The sealed capillary is then cooled to effect crystallization of the sulfoxide.

9 This procedure, with slight modifications depending on the physical properties of the sulfide and sulfoxide in question, has been used to prepare a variety of sulfoxides as illustrated by examples provided in Table I. In the case of very insoluble sulfides, co solvents such as methanol or dioxane may be employed. Very

TABLE I
PREPARATION OF SULFOXIDES

Products	Yields, %	M P [B P], °C
Methyl 4 ketopentyl sulfoxide	98	22.5–23.5 [99–101 (0.12 mm)]
Thian 1 oxide	99	67–68
1,4 Oxathian 1 oxide	83	46–47
Bis(2-diethylaminoethyl)sulfoxide	85	Dipicrate 146–148
Acetoxymethyl methyl sulfoxide	72	[85–90 (0.1 mm)]
1-Benzylsulfinyl 2 propanone	89	126.0–126.5
Phenylsulfinylacetic acid	99	118.0–119.5
Benzyl sulfoxide	96	135–136
Ethyl sulfoxide	65	[45–47 (0.15 mm)]
Ethyl phenyl sulfoxide	93	[101–102 (1.5 mm)]

soluble sulfoxides are best isolated by continuous extraction with chloroform or methylene chloride.

3. Methods of Preparation

Methyl phenyl sulfoxide has also been prepared from thioanisole by the action of hydrogen peroxide,^{2, 3} lead tetraacetate,⁴ and dinitrogen tetroxide,^{5, 6} and from methanesulfinyl chloride and benzene with anhydrous aluminum chloride.⁷

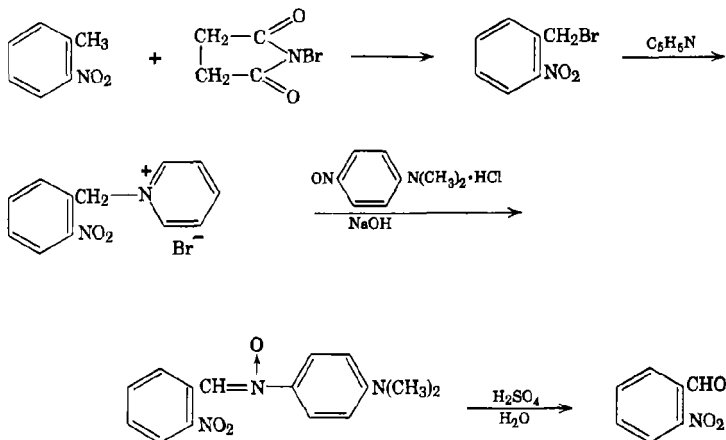
4. Merits of the Preparation

The present procedure is a specific example of the method generalized by Leonard and Johnson.⁸ The method employs extremely mild reaction conditions and affords high yields of sulfoxides (Note 9) free of contamination by sulfides or sulfones. Sodium periodate is easily and safely handled; however, the higher cost of this reagent in comparison to certain other oxidants, *e.g.*, hydrogen peroxide, may prohibit its use in large-scale reactions.

1. Department of Chemistry, Wayne State University, Detroit, Michigan This work was supported in part by grant GP-1159 of the National Science Foundation.
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o-NITROBENZALDEHYDE

(Benzaldehyde, o-nitro-)

Submitted by A. KALIR¹Checked by JOHN H. SELLSTEDT, WAYLAND E. NOLAND,
and WILLIAM E. PARHAM**1. Procedure**

A. *o*-Nitrobenzylpyridinium bromide. A 1-l. flask fitted with a reflux condenser is charged with 102 g. (0.744 mole) of *o*-nitrotoluene, 120 g. (0.675 mole) of N-bromosuccinimide, 1.0 g. of benzoyl peroxide, and 450 ml. of dry carbon tetrachloride. The mixture is heated under reflux until, after the refluxing is temporarily interrupted, all the solid is seen to float on the surface (usually 6–8 hours suffices).

The hot mixture is filtered with suction into a 1-l. round-bottomed flask through a Büchner-type sintered glass funnel provided with a ground joint (Note 1). The solid on the funnel is washed successively with two 50-ml portions of hot carbon

tetrachloride. The solvent is removed from the filtrate under reduced pressure on a water bath (Note 2). The flask is then fitted with a reflux condenser, and 400 ml. of commercial absolute ethanol and 65 ml. (0.81 mole) of good grade pyridine (Note 3) are added to the residue.

The solution is heated at the reflux temperature for 45 minutes and immediately transferred to a wide-mouthed Erlenmeyer flask. Crystallization begins at once, and, after the mixture is cooled, the crystals of nearly pure *o*-nitrobenzylpyridinium bromide are collected, washed with cold ethanol, and used in the next step (Note 4).

B. *N*-(*p*-Dimethylaminophenyl)- α -(*o*-nitrophenyl)nitrone. The wet *o*-nitrobenzylpyridinium bromide, together with 100 g. (0.536 mole) of *p*-nitrosodimethylaniline hydrochloride (Note 5) and 800 ml. of ethanol are introduced into a 2-l. three-necked flask equipped with an efficient stirrer, thermometer, and a dropping funnel, and immersed in an ice-salt bath. The stirrer is started, and a solution of 54 g. (1.35 mole) of sodium hydroxide in 500 ml. of water is added at 0–5° (Note 6). The color changes gradually from yellow to green, brown, and orange. The stirring is continued at 5–10° over a period of 1 hour. At the end of this time 500 ml. of ice-cold water is added to the flask, and the orange *N*-(*p*-dimethylaminophenyl)- α -(*o*-nitrophenyl)nitrone is collected on a large Büchner funnel, pressed well, and washed with cold water. The nitrone is used in the next step without further purification (Note 7).

C. *o*-Nitrobenzaldehyde. The wet crude nitrone is placed in a 3-l. beaker. A hot solution of approximately 6*N* sulfuric acid (Notes 8, 9) is then added, and the mixture is hand-stirred with a spatula or a glass rod. Crushed ice is added after 10 minutes, and the crude solid *o*-nitrobenzaldehyde is filtered, washed successively with dilute sodium bicarbonate solution and water, and dried over calcium chloride in a desiccator.

The brown material is best purified by distillation under reduced pressure. The yellow aldehyde is collected at 120–140° (3 mm.) (Note 10) and melts at 41–44°. This material weighs 48–54 g. (47–53% overall yield based on *N*-bromosuccinimide) and is sufficiently pure for most uses (Notes 11, 12).

2. Notes

1. Suction filtration is necessary. The filtration is conveniently carried out through a regular Büchner funnel connected through a rubber stopper to a 1-l. suction flask. *Since o-nitrobenzyl bromide is a powerful lachrymator, the filtration should be carried out in a fume hood.*

2. The checkers used a rotary evaporator.

3. The checkers used Merck Reagent A.C.S. grade pyridine.

4. The yield of air-dried *o*-nitrobenzylpyridinium bromide is 125–135 g. (63–68%). The product melts at 206–208° (cor.).

5. Freshly prepared *p*-nitrosodimethylaniline hydrochloride² was used without further purification.

6. Sometimes a difficulty in stirring is encountered, and 100–200 ml. of ethanol should be added to the reaction mixture. The checkers found that the reaction mixture became a very thick paste which was quite difficult to stir. Use of a sturdy Hershberg stirrer is recommended.

7. The wet material contains about 55–65% of water. When the product is dried in a vacuum desiccator and recrystallized from ethyl acetate or acetone, it melts at 130–134°.

8. The solution is prepared by careful addition of 170 ml. of concentrated sulfuric acid to 850 ml. of water.

9. Hydrochloric acid (15%) can be substituted for sulfuric acid with equal results.

10. The checkers collected the product at 97–99° (1 mm.).

11. Very pure material can be obtained by dissolving *o*-nitrobenzaldehyde in toluene and precipitating with petroleum ether, according to earlier instructions.³

12. The same yields are obtained when the scale of this preparation is doubled.

3. Methods of Preparation

o-Nitrobenzaldehyde has been prepared by numerous methods.³ The best-known and most widely used route involves the oxidation of *o*-nitrotoluene by chromium trioxide in acetic anhydride-acetic acid solution.³ The present preparation is an example of

the Kröhnke reaction.⁴ It is adapted from the published directions for the synthesis of a series of halo- and nitrobenzaldehydes.⁵

4. Merits of the Preparation

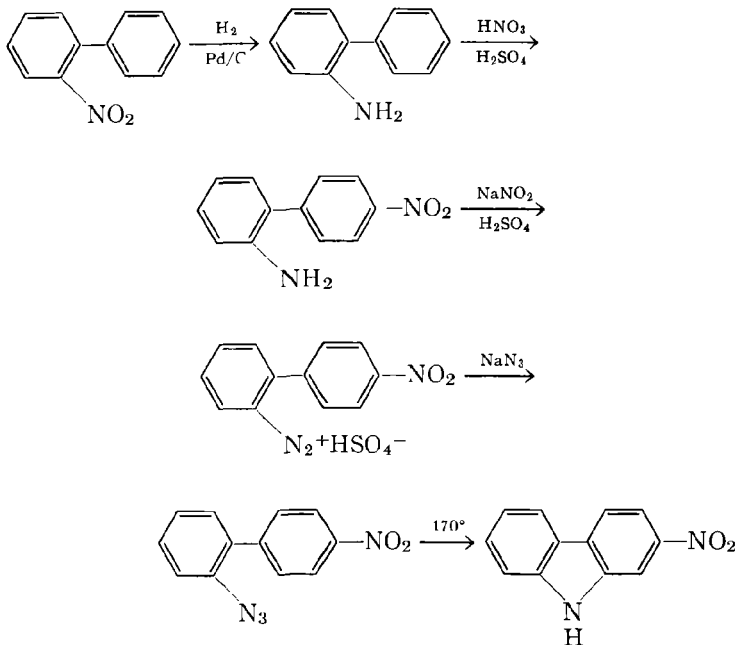
The present procedure is a general method for preparing aromatic and heterocyclic aldehydes. It is of particular value in the synthesis of *o*-nitrobenzaldehydes in 100–200 g. lots. The benzaldehydes are useful starting materials for cinnamic acids, β -nitrostyrenes, etc. The manipulations are simple, the yields are reproducible, and the intermediates can be easily isolated and purified. The intermediates themselves have many synthetic uses.

The submitter has prepared the fluoro-*o*-nitrobenzaldehydes shown in Table I by application of this method.

TABLE I
FLUORO-*o*-NITROBENZALDEHYDES

Position of Fluorine	M P of Fluoro-2-nitrobenzylpyridinium Bromide, °C	M. P. of N-(<i>p</i> -dimethylaminophenyl)- α -(fluoro- <i>o</i> -nitrophenyl)nitron, °C	M P of Aldehyde, °C	Overall Yield, %
4	200–201	164–165	32–33	55–62
5	189–190	155–156	93–95	45–55
6	202–204	151–152	62–63	59–66

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5. K Clarke, *J Chem Soc*, 3807 (1957)

2-NITROCARBAZOLE**(Carbazole, 2-nitro-)**Submitted by G. DAVID MENDENHALL and PETER A. S. SMITH¹

Checked by HOWARD A. HARRIS and KENNETH B. WIBERG

1. Procedure

A. o-Aminobiphenyl. A Parr bottle is charged with 60 g. (0.30 mole) of *o*-nitrobiphenyl (Note 1), 3 g. of 5% palladium-on-carbon catalyst (Note 2), and 200 ml. of 95% ethanol. The mixture is shaken with hydrogen under 25–50 p.s.i. until the gas is no longer absorbed (about 70 minutes), the catalyst is filtered from the hot solution and washed with 20 ml. of ethanol, and the filtrates are poured in a thin stream into 1 l. of ice water contained

in a 2-l. Erlenmeyer flask (Note 3). After standing for 20 minutes the white solid is filtered with suction, pressed to remove excess water, and allowed to dry in air. The yield of essentially pure *o*-aminobiphenyl is 48–51 g. (94–100%), m.p. 43–45.5°.

B. *o*-Amino-*p*'-nitrobiphenyl. Concentrated sulfuric acid (400 ml.) is placed in a 1-l. round-bottomed flask fitted with a mechanical stirrer and a thermometer. Stirring is begun, and 45.0 g. (0.27 mole) of powdered *o*-aminobiphenyl is added all at once through a powder funnel. When the amine has dissolved, the flask is placed in an ice-salt bath and its contents cooled to a temperature between 0° and –5°. A mixture of 30 ml. of concentrated sulfuric acid and 11.0 ml. of fuming nitric acid (density 1.5) is then added dropwise from a separatory funnel while the temperature is kept below 0°. The addition requires about an hour, and stirring is continued 45 minutes longer. The liquid is poured onto 1.5 kg. of ice in a 4-l. beaker and treated carefully until neutral with a solution of 580 g. (14.5 moles) of sodium hydroxide in 1.5 l. of water cooled to room temperature. The resultant hot suspension of product is allowed to cool nearly to room temperature, filtered with suction, and the orange solid is washed with 500 ml. of water. The crude material is pressed free of excess water and recrystallized from 850–1000 ml. of 95% ethanol (Note 4), giving 32–42 g. (56–74%) of orange needles, m.p. 156–158.5°.

C. *o*-Azido-*p*'-nitrobiphenyl. Water (100 ml.) is placed in a 1-l. round-bottomed flask equipped with a thermometer and an efficient mechanical stirrer. With stirring, 30 ml. of concentrated sulfuric acid is added, followed by 32.1 g. (0.15 mole) of recrystallized *o*-amino-*p*'-nitrobiphenyl. When all the amine has been converted to the white sulfate, 50 ml. more of water is added and the suspension is cooled to 0–5° in an ice-salt bath. A solution of 11 g. (0.16 mole) of sodium nitrite in 30 ml. of water is added dropwise over a period of 15 minutes (Note 5), and the mixture is stirred for 45 minutes longer. A thick precipitate of the sparingly soluble diazonium salt may have separated from the initially clear solution by this time. With strong stirring, a solution of 12 g. (0.17 mole) of sodium azide in 40 ml. of water is run in (Note 6), and stirring is continued for 40 minutes longer. The

thick white solid is filtered with suction and washed with 200 ml. of water. After pressing free of excess water, the material is allowed to dry in air in a dark place. The yield of gray-white azide is 35.5–36 g. (99–100%), m.p. 91.5–92.5° (Note 7).

D. *2-Nitrocarbazole*. In a 2-l. round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a short air condenser are placed 35.5 g. (0.15 mole) of powdered *o*-azido-*p*'-nitrobiphenyl and 1 l. of *o*-dichlorobenzene (Note 8). The stirred mixture is heated above 170° for 1 hour by means of a heating mantle, allowed to cool to room temperature, and chilled in a refrigerator (5°) for several hours. The crude product is filtered with suction, washed with 40 ml. of light petroleum, and sucked dry on the filter. There results 26–28 g. of yellow-brown crystals, m.p. 171.5–174°. The filtrate is distilled under aspirator pressure to a volume of 150–200 ml. and chilled as before, to yield an additional 2–3 g., m.p. 171–174°. The total yield is 28–30 g. (89–96%). The combined crops are dissolved in 400–450 ml. of boiling 95% ethanol with 3–4 g. of Norit® to remove impurities and filtered through a preheated Büchner funnel. The filtrate on cooling deposits bright yellow needles of product, which are filtered after standing at 5° for several hours. This crop weighs 23–25 g., m.p. 174–175.5°. Concentration of the mother liquor to a small volume (50–70 ml.) and chilling gives a second crop of lesser purity, 1–2 g., m.p. 172–175°. The total yield of recrystallized material is 24–26.5 g. (77–85%), and the overall yield from *o*-nitrobiphenyl is 40–63%.

2. Notes

1. An Eastman Kodak technical grade of *o*-nitrobiphenyl was used by the submitters. This is no longer available, and the checkers used the material supplied by K and K Laboratories.
2. The Baker Co. catalyst was used.
3. This carcinogen is more easily handled in a flask than in a beaker. Contact with the skin obviously should be avoided.
4. Recrystallization is best accomplished by adding the compound to boiling ethanol and filtering. Prolonged heating should be avoided, as the substance gradually decomposes in hot solvent.

5. The sodium nitrite solution must be added carefully in order to avoid loss of material due to vigorous foaming.

6. This operation should be carried out in a hood to avoid the unpleasant effects of exposure to hydrogen azide vapors.

7. The compound may be recrystallized from a large volume of ethanol, but no increase in yield was noted using recrystallized material in the next step.

8 Eastman Kodak *o*-dichlorobenzene of 95% purity was used. Olefin-free kerosene or decalin may be substituted for the solvent, keeping the reaction temperature between 170° and 190°.

3. Methods of Preparation

o-Aminobiphenyl has been prepared by the reduction of the corresponding nitro compound with zinc and acetic acid,² zinc and hydrochloric acid,³ iron and hydrochloric acid,⁴ sodium bisulfite under pressure,⁵ or hydrazine and palladium,⁶ by the Hofmann reaction on *o*-phenylbenzamide,⁷ and by pyrolysis of diazoaminobenzene.^{8, 9}

o-Amino-*p*'-nitrobiphenyl has been made by the nitration of *o*-aminobiphenyl with ethyl nitrate,¹⁰ by hydrolysis of the corresponding acetamide derivative,^{11, 12} and by partial reduction of *o*, *p*'-dinitrobiphenyl with sodium bisulfite under pressure.⁵

2-Nitrocarbazole has been prepared by the dehydrogenation of 2-nitro-1,2,3,4-tetrahydrocarbazole with chloranil,¹³ by the deamination of 2-nitro-3-aminocarbazole,¹⁴ and by the thermal decomposition of *o*-azido-*p*'-nitrobiphenyl.¹⁵ The procedure given here is a slight modification of the last-mentioned method.

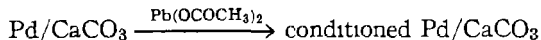
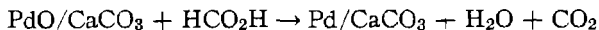
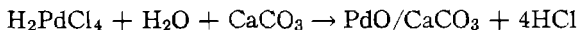
4. Merits of the Preparation

The decomposition of *o*-azidobiphenyls is a convenient and general synthesis for a variety of carbazoles in good yield,¹⁶ especially those not available through direct substitution of carbazole itself. Many of the required intermediates can be prepared from *o*-aminobiphenyl by substitution reactions. The method is also applicable to the preparation of analogs of the carbazole system in which a heterocyclic ring replaces a benzene

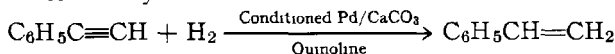
ring, to the preparation of indoles, and to certain analogous aliphatic systems.

- 1 Department of Chemistry, University of Michigan, Ann Arbor, Michigan
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P A S Smith and J H Hall, *J Am Chem Soc*, **84**, 480 (1962)

PALLADIUM CATALYST FOR PARTIAL REDUCTION OF ACETYLENES¹



Test for selectivity



Submitted by H LINDLAR and R DUBUIS²

Checked by F. N JONES and B C MCKUSICK

1. Procedure

Palladous chloride (1.48 g, 0.0083 mole) (Note 1) is placed in a 10-ml. Erlenmeyer flask, and 3.6 ml. (0.043 mole) of 37% hydrochloric acid is added. The flask is shaken at about 30° until the palladous chloride is dissolved. The chloropalladous acid solution is transferred to a 150-ml. beaker with 45 ml of

distilled water (Note 2). The beaker is equipped with a pH meter and a magnetic or mechanical stirrer. The pH of the stirred solution is brought to 4.0–4.5 by slow addition of aqueous 3*N* sodium hydroxide from a buret. A precipitate may form at high local concentrations of sodium hydroxide, but it dissolves on further stirring. The solution is diluted to approximately 100 ml. in a graduated cylinder and placed in a 200-ml. or 250-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer and a thermometer and partly immersed in a bath of oil or water. Precipitated calcium carbonate (18 g.) (Note 3) is added. The well-stirred suspension is heated to 75–85° and held at this temperature until all the palladium has precipitated, as indicated by loss of color from the solution; this takes about 15 minutes. With the mixture still at 75–85°, 6.0 ml. of sodium formate solution (about 0.7*N*) (Note 4) is added. During the addition CO₂ escapes and the catalyst turns from brown to gray; rapid stirring is essential to keep the mixture from foaming over. An additional 4.5 ml. of the sodium formate solution is added, and the reduction is completed by stirring the mixture at 75–85° for 40 minutes. The catalyst, which is now black, is separated on a 10-cm. Büchner funnel (Note 5) and washed with eight 65-ml. portions of water.

The moist catalyst is placed in a 200-ml. or 250-ml. round-bottomed flask equipped as described above. Water (60 ml.) and 18 ml. of a 7.7% solution of lead acetate (Note 6) are added. The slurry is stirred and heated at 75–85° for 45 minutes. The catalyst is separated on a 10-cm. Büchner funnel, washed with four 50-ml. portions of water, sucked as dry as possible, and dried in an oven at 60–70° (Note 7). The dried catalyst, a dark gray powder, weighs 19–19.5 g. (Note 8).

To establish that the catalyst is active and selective, it is convenient to test it by quantitative hydrogenation of phenylacetylene to styrene. The reaction flask of a low-pressure hydrogenation apparatus (Note 9) is charged with 2.04 g. (0.0200 mole) of phenylacetylene, 0.10 g. of the palladium catalyst, 1.0 ml. of quinoline (Note 10), and 15 ml. of olefin-free petroleum ether (b.p. 80–105°) or hexane (Note 11). The apparatus is evacuated, and hydrogen is admitted to a pressure slightly above 1 atm.

Stirring or shaking is started, causing rapid absorption of hydrogen. The hydrogen pressure is kept close to 1 atm. Absorption of the first 0.0200 mole of hydrogen requires 10–90 minutes, depending on the activity of the catalyst. Hydrogen absorption then abruptly slows but does not stop. In synthetic work it is desirable to stop the reaction soon after the required amount of hydrogen has been absorbed.

2. Notes

1. Palladium chloride, Engelhard, 60% Pd, was obtained from Engelhard Industries, 113 Astor Street, Newark 14, New Jersey.

2. All water used in the procedure should be distilled or deionized water or chlorine-free tap water.

3. A commercial grade of "precipitated" (not "powdered" or "prepared") calcium carbonate is satisfactory, if it can be filtered easily. The checkers used Fisher Catalog No. C-62 Calcium Carbonate, U.S.P. (Precipitated Chalk).

4. To prepare the sodium formate solution, a filtered solution of 15 g. (0.14 mole) of anhydrous sodium carbonate in 80 ml. of water is diluted to 120 ml. Approximately 4 ml. (4.9 g., 0.10 mole) of 99% formic acid (a commercial grade) is then added dropwise until the solution is weakly alkaline to phenolphthalein.

5. The checkers found a funnel with a fritted disk convenient. Thorough washing is essential.

6. The solution is prepared by dissolving 9.0 g. (0.024 mole) of a commercial grade of lead acetate, $\text{Pb}(\text{OCOCH}_3)_2 \cdot 3\text{H}_2\text{O}$, in 100 ml. of water.

7. The checkers dried the catalyst for 2 hours in a vacuum oven at 60° (1 mm.).

8. The catalyst has been stored for more than 3 years with no loss in activity.

9. The hydrogen pressure and the design of the apparatus are not critical; any apparatus in common use is satisfactory. The checkers used an apparatus having a magnetically stirred reaction flask as described by Wiberg.³

10. Less quinoline (as little as 5% of the weight of the catalyst) often suffices for hydrogenations of this type.

11. Benzene, toluene, or acetone may be used as solvent for substances insoluble in paraffins. Alcohols are usually unsatisfactory media.

3. Methods of Preparation

The preparation of the catalyst is a slight modification of the original procedure.⁴

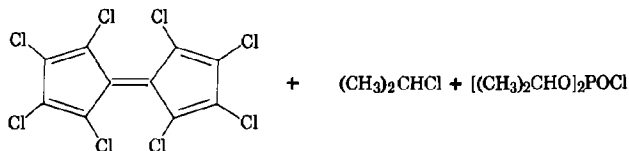
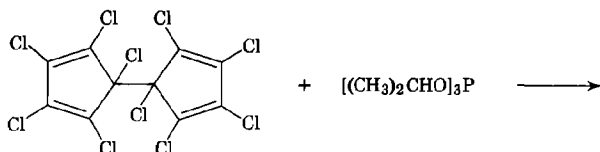
4. Merits of the Preparation

This form of palladium can be used for the hydrogenation of almost any triple bond to the double bond. Reduction of doubly substituted acetylenes gives *cis* olefins.

1. Checkers' note: Among organic chemists this catalyst is commonly called "Lindlar catalyst."
2. Chemical Research Department, F. Hoffmann-LaRoche & Co. Ltd., Basel, Switzerland.
3. K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Company, New York, 1960, pp. 228-230.
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PERCHLOROFULVALENE

(Bicyclopentadienylidene, octachloro-)

Submitted by V. MARK¹

Checked by M. ROSENBERGER and PETER YATES

1. Procedure

A slurry of 47.5 g. (0.100 mole) of decachlorobi-2,4-cyclopentadienyl (Note 1) in 200 ml. of petroleum ether (b.p. 30–60°) is prepared in a 1-l., three-necked, round-bottomed flask equipped with a Hershberg stirrer, thermometer, dropping funnel, and air condenser fitted with a drying tube. The reaction flask is immersed in a water bath at 20–24° and the stirrer is started. A solution of 25.2 g. (0.121 mole) of triisopropyl phosphite (Note 2) in 25 ml. of petroleum ether (b.p. 30–60°) is added from the dropping funnel at such a rate that the temperature of the mildly exothermic reaction remains between 20° and 25°. During the addition, which requires 50–80 minutes, the light yellow slurry of the starting material is converted to a dark blue slurry of perchlorofulvalene.

After the addition is completed, the reaction mixture is stirred for an additional period of 20 minutes. The crystalline product

is filtered rapidly by suction through a sintered-glass funnel (Note 3) and rapidly washed with three 20-ml. portions of petroleum ether (b.p. 30–60°). After the last washing, the perchlorofulvalene is allowed to dry at room temperature. The yield of the dark bluish-violet, uniform crystals is 26–29 g. (65–72%). The chlorocarbon is of a high purity, as indicated by infrared and ultraviolet spectroscopy (Note 4); it can be recrystallized from benzene, cyclohexane, hexane, carbon tetrachloride, or methylene chloride without appreciable lowering of the yield.

2. Notes

1. Decachlorobi-2,4-cyclopentadienyl [bis-(pentachlorocyclopentadienyl)], m.p. 123–124°, can be obtained from Columbia Organic Chemicals Co., Inc., and Aldrich Chemical Co., Inc. The checkers used purified material, m.p. 124–126°, obtained by recrystallization of commercial material from hexane. They found that without prior purification of the commercial starting materials or correction for assay (cf. Note 2) the yield was reduced to 50%. The checked runs were carried out under nitrogen, but it was not determined whether this influenced the yield.

2. Triisopropyl phosphite can be obtained from Virginia Carolina Chemical Corporation, Eastman Organic Chemicals, Aldrich Chemical Company, Matheson Coleman and Bell, and K and K Laboratories. The presence of diisopropyl hydrogen phosphite or triisopropyl phosphate is not deleterious, but a correction for the assay is required. Fractionation readily separates triisopropyl phosphite, b.p. 60–61° (10 mm.), from diisopropyl hydrogen phosphite, b.p. 70–71° (10 mm.), and triisopropyl phosphate, b.p. 95–96° (10 mm.). The checkers used a fraction, b.p. 85–88° (33 mm.) (cf. Note 1).

Alternatively, triethyl phosphite (available from the suppliers given above) can be substituted, in equivalent amount, for triisopropyl phosphite; the yield of perchlorofulvalene is 55–60%. The use of trimethyl phosphite gives lower yields (45–48%) and a less pure product.

3. The use of a large-size (500-ml.), coarse-grade, sintered-glass funnel permits rapid filtration and the washing of the filter cake

directly in the funnel. Rapid removal of the co-product, diisopropyl phosphorochloridate, $(C_3H_7O)_2P(O)Cl$, from perchlorofulvalene is necessary in order to prevent its hydrolysis to petroleum ether-insoluble products.

4. Since perchlorofulvalene does not melt below its decomposition point around 200° , infrared and ultraviolet spectroscopic analyses provide the most satisfactory method of checking the purity of the product. The characteristic infrared maxima of perchlorofulvalene occur at 6.55, 7.56, 7.97, 8.10, 8.63, 10.37, 13.03, 14.24, and $14.53\ \mu$. and the ultraviolet and visible maxima at $386\ m\mu$ (ϵ 35,800) and $590\ m\mu$ (ϵ 505). The absence of decachlorobi-2,4-cyclopentadienyl in the product is indicated by the absence of its characteristic bands at 6.27, 12.35, and $14.83\ \mu$.

3. Methods of Preparation

The present procedure is that described by the submitter.² Perchlorofulvalene has also been obtained in 57% yield by the catalytic dechlorination of decachlorobi-2,4-cyclopentadienyl at 500° and 0.1 mm.³

4. Merits of the Preparation

Perchlorofulvalene is the only stable compound known at present in which the fulvalene system alone represents all the unsaturation. The current listing of a compound as "perchlorofulvalene" in various chemical catalogs is based on earlier work shown to be in error;² this compound has been shown to be a $C_{15}Cl_{12}$ chlorocarbon with a trindane skeleton.²

Perchlorofulvalene is a highly reactive chlorocarbon which undergoes a variety of reactions, including dimerization and addition reactions, especially with nucleophiles. It has a unique structure⁴ which reflects a compromise between steric hindrance and conjugation. The method of preparation exemplifies the use of the mild dehalogenating properties of alkyl phosphites.

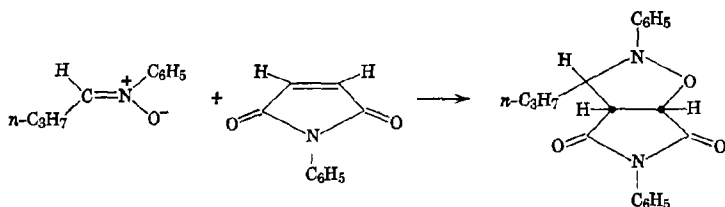
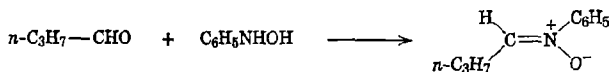
1. Hooker Chemical Corporation, Research Center, Niagara Falls, New York.

2. V. Mark, *Tetrahedron Letters*, 333 (1961).

3. A. E. Ginsberg, R. Paatz, and F. Korte, *Tetrahedron Letters*, 779 (1962).

4. P. J. Wheatley, *J. Chem. Soc.*, 4936 (1961).

**2-PHENYL-3-*n*-PROPYLISOXAZOLIDINE-4,5-*cis*-
DICARBOXYLIC ACID N-PHENYLMIDE**



Submitted by INGRID BRÜNING, RUDOLF GRASHEY, HANS HAUCK,
ROLF HUISGEN, and HELMUT SEIDL¹
Checked by ROBERT ELIASON, WAYLAND E. NOLAND,
and WILLIAM E. PARHAM

1. Procedure

N-Phenylhydroxylamine (11 g., 0.10 mole)² (Note 1) and N-phenylmaleimide (17.4 g., 0.10 mole)³ are suspended in 40 ml. of ethanol contained in a 200-ml. Erlenmeyer flask. To the mixture is added immediately (Note 2) 8.98 g. (11.2 ml., 0.124 mole) of freshly distilled *n*-butyraldehyde. An exothermic reaction ensues, and the mixture spontaneously heats to the boiling point. A clear slightly yellow solution results which, upon cooling, deposits an almost colorless crystalline cake. The mixture is allowed to stand in the ice box for 1 day; it is then filtered through a Büchner funnel, and the crystals are washed twice with 25-ml. portions of ice-cold ethanol. The yield of air-dried product, m.p. 99–101°, is 31–32 g. (92–95%). For further purification the crude material is dissolved in 60 ml. of boiling ethanol on the steam bath, and the resulting solution is allowed to cool slowly to room temperature. If crystallization does not spontaneously begin in 5–10 minutes, it can then be induced by

seeding. After being kept for 5 hours in the refrigerator, the solution is filtered and the colorless crystals are washed twice with 20-ml. portions of cold ethanol. The dried product weighs 29–30 g. An additional recrystallization of the air-dried product from 60 ml. of ethanol gives 26–27 g. (77–80%) of the pure isoxazolidine, m.p. 106.5–107.5°.

2. Notes

1. The phenylhydroxylamine should be free of sodium chloride. This can be easily removed by dissolution of the substance in benzene followed by filtration, and then addition of petroleum ether to precipitate the pure compound.

2. The checkers observed, in two runs, that when *n*-butyraldehyde is added after 10–15 minutes, the reaction is only mildly exothermic, and the white precipitate that forms does not dissolve. The infrared spectrum of the white crystalline product (19–20 g., m.p. 181–184° dec.) suggests that it may be the adduct of phenylhydroxylamine and N-phenylmaleimide formed by addition of the N—H bond of the amine to the olefinic bond of the imide; however, the structure of the product was not further examined.

3. Methods of Preparation

The preparation of 2-phenyl-3-*n*-propylisoxazolidine-4,5-*cis*-dicarboxylic acid N-phenylimide from *n*-butyraldehyde, N-phenylhydroxylamine, and N-phenylmaleimide is new and is described by Hauck.⁴ The intermediate, C-(*n*-propyl)-N-phenylnitrone, is an unstable compound and is difficult to purify. The procedure described avoids the isolation of the nitrone by adding it *in situ* to a suitable dipolarophile.

4. Merits of the Preparation

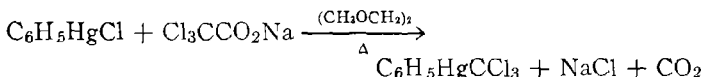
The present procedure serves as a model for the generation and use *in situ* of unstable nitrones in 1,3-dipolar cycloaddition reactions.

1. Institut für Organische Chemie der Universität München, München, Germany.
2. O. Kamm, *Org. Syntheses*, Coll. Vol. 1, 445 (1941).

- 3 M. P Cava, A A Deana, K Muth, and M. J. Mitchell, *Org Syntheses*, **41**, 93 (1961).
4. H. Hauck, Dissertation, Universitat Munchen, 1963.

PHENYLTRICHLOROMETHYLMERCURY

[Phenyl(trichloromethyl)mercury]



Submitted by TED J LOGAN¹

Checked by WILLIAM E PARHAM and JOHN R. POTOSKI

1. Procedure

Into a 250-ml. round-bottomed flask equipped with a magnetic stirrer and reflux condenser fitted with a drying tube containing Drierite® are placed 150 ml. of dimethoxyethane (Note 1), 27.8 g. (0.15 mole) of sodium trichloroacetate (Note 2), and 31.3 g. (0.1 mole) of phenylmercuric chloride. The stirred mixture (Note 3) is heated to reflux (~85°) by use of a heating mantle. Carbon dioxide evolution, which begins shortly after heating is begun, is accompanied by the appearance of a precipitate of sodium chloride. The reactants are heated at the reflux temperature until no more carbon dioxide evolution is obvious (~1 hour), then cooled to room temperature and poured into 500 ml. of water. The resulting mixture, consisting of a dense oil layer, a solid, and an aqueous layer, is extracted with four 50-ml. portions of diethyl ether. The combined ether layers are then washed with two 50-ml. portions of water, dried over anhydrous magnesium sulfate, filtered, and the solvent removed using a rotary evaporator. The resulting white solid, which weighs 44.8 g., is dissolved in 130 ml. of hot chloroform and fractionally crystallized. The first three fractions weigh 2.3 g. and are recovered phenylmercuric chloride. Successive reduction of solvent volume and further fractional crystallization provides 25.6 g. of product (65% yield), m.p. 110° (Notes 4 and 5).

2. Notes

1. The 1,2-dimethoxyethane (monoglyme) was purchased from Matheson Coleman and Bell and purified by distillation from lithium aluminum hydride. The use of unpurified solvent had little effect on the yield of product.

2. Sodium trichloroacetate may be purchased from the Dow Chemical Company (96.4% pure by Cl analysis) or prepared by neutralizing trichloroacetic acid (Matheson Coleman and Bell) with aqueous sodium hydroxide to the phenolphthalein end point. The product is dried under vacuum for 12 hours, sieved, then dried an additional 12 hours under vacuum, all at room temperature. The salt prepared by this method and used in this preparation was 98.5% pure, based on chlorine analysis, and can be stored indefinitely without decomposition. The submitter has obtained nearly identical yields of phenyltrichloromethylmercury from the commercial and from the prepared salts.

3. If all the reactants are stirred for several minutes at room temperature, they dissolve to give a turbid solution. Stirring while heating then becomes unnecessary, except to promote more even heating, since the refluxing solvent and carbon dioxide evolution keep the precipitated sodium chloride in suspension.

4. Purity of the product was ascertained by quantitative X-ray fluorescence analysis for chlorine and mercury, which showed satisfactory agreement with calculated values. Compounds containing both mercury and chlorine are difficult to analyze by classical "wet" analytical procedures.

5. Yields as high as 77% have been obtained by this procedure. It is difficult to recover all the product from the mother liquor. The use of a 1:1 ratio of sodium trichloroacetate and phenylmercuric chloride gave yields of 39–45%, while a 1.25:1 ratio gave a 61% yield of product.

3. Methods of Preparation

This procedure is essentially identical with that previously published by the submitter.²

The pyrolysis of sodium trichloroacetate in 1,2-dimethoxy-

ethane was originally described by Wagner³. Razuvaev later adapted this procedure to the synthesis of organomercurials, including the title compound.⁴

Phenyltrichloromethylmercury has also been prepared by the reaction of phenylmercuric bromide with sodium methoxide and ethyl trichloroacetate⁵ (62–71% yield); of phenylmercuric chloride with potassium *t*-butoxide and chloroform⁶ (52% yield), of phenylmagnesium bromide with trichloromethylmercuric bromide⁷ (24% yield); of trichloromethylmercuric bromide with diphenyldichlorotin (49%), and of trichloromethylmercuric bromide with phenylmagnesium bromide⁸ (no yield given).

4. Merits of the Preparation

The main advantages of this procedure are simplicity of apparatus and technique, availability of reactants, ease of product isolation in good yield, and purity of product. The submitter has also used this method successfully for the preparation of trichloromethylmercuric chloride (from mercuric chloride), bis-(trichloromethyl)mercury (from a 2:1 ratio of sodium trichloroacetate to mercuric chloride or mercuric acetate), and trichloromethylmercuric bromide (from mercuric bromide).

Phenyltrihalomethylmercurials, including the title compound, can be thermally decomposed in the presence of olefins to yield the corresponding dichlorocyclopropane derivatives.^{2, 9–11} Olefins such as tetrachloroethylene and ethylene, which give exceptionally low yields of dichlorocyclopropanes when treated with other reagents for generating dichlorocarbene ($:CCl_2$), give reasonable yields of dichlorocyclopropanes when heated with phenyltrichloromethylmercurials.¹²

These mercurials have also been employed in the preparation of dihalomethyl derivatives of carbon, silicon, and germanium.¹³

1 The Procter and Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio

2 T. J. Logan, *J. Org. Chem.*, **28**, 1129 (1963)

3 W. M. Wagner, *Proc. Chem. Soc.*, 229 (1959)

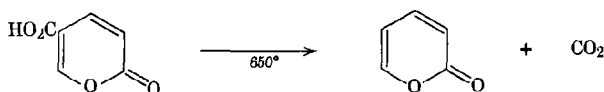
4 G. A. Razuvaev, N. S. Vasilevskaya and L. A. Nikitina, *Tr. po Khim. i Khim. Tekhnol.*, **3**, 638 (1960) [*C.A.*, **56**, 15116d (1962)]

5 E. E. Schweizer and G. J. O'Neill, *J. Org. Chem.*, **28**, 851 (1963)

- 6 O A Reutov and A N Lovtsova, *Dokl Akad Nauk SSSR*, **139**, 622 (1961) [*C A* , **56**, 1469b (1962)], *Izv Akad Nauk SSSR, Old Khim Nauk*, 1716 (1960) [*C A* , **55**, 9319h (1961)]
- 7 R Kh Freidlina and F K Velchko, *Izv Akad Nauk SSSR, Old Khim Nauk*, 1225 (1959) [*C A* , **54**, 1379g (1960)]
- 8 A N Nesmeyanov, R Kh Freidlina, and F K Velchko, *Dokl Akad Nauk SSSR*, **114** 557 (1957) [*C A* **52**, 296d (1958)]
- 9 D Seyferth, J M Burlitch, and J K Heeren, *J Org Chem* , **27**, 1491 (1962)
- 10 D Seyferth and J M Burlitch, *J Am Chem Soc* , **84**, 1757 (1962)
- 11 D Seyferth and J M Burlitch, *J Am Chem Soc* , **86**, 2730 (1964)
- 12 D Seyferth, R J Minas, A J H Treiber, J M Burlitch, and S R Dowd, *J Org Chem* , **28**, 1163 (1963)
- 13 D Seyferth and J M Burlitch, *J Am Chem Soc* , **85**, 2667 (1963)

α -PYRONE

(2-Oxo-1, 2H-pyran-)



Submitted by HOWARD E ZIMMERMAN, GARY L GRUNEWALD,
and ROBERT M PAUFLER¹

Checked by E J COREY, W H PIRKLE, and M J HADDADIN

1. Procedure

A 37.5-g. (0.266-mole) sample of coumalic acid (Note 1) is placed in a 30 x 10 cm. cylindrical flask attached horizontally to a 55 x 3 cm oven-heated Vycor tube (Note 2) *loosely* packed with 20 g. of fine copper turnings (Note 3). Following the Vycor tube successively are two ice-cooled 50-ml. receivers and a dry ice trap. The latter is connected to an efficient vacuum pump (Note 4). The system is evacuated, and the Vycor tube is heated to 650–670°. Then the flask containing the coumalic acid is heated with a nichrome wound heating jacket to 180°, and the temperature is allowed to rise slowly to 215°. During this time coumalic acid sublimes into the Vycor tube and α -pyrone distills into the ice-cooled receivers. The pressure is held below 5 mm (Note 5). The yield of pale yellow crude material is 18–19 g. (70–75%).

Distillation affords 16.9–18 g. (66–70%) of colorless oily α -pyrone, b.p. 110° (26 mm.), n_D^{25} 1.5270.

2. Notes

1. Coumalic acid, m.p. 206–209°, was prepared by the method of Wiley and Smith² and recrystallized from methanol as described. Starting material prepared in this way still contains impurities but is satisfactory for the preparation of α -pyrone. A purer grade of colorless coumalic acid, m.p. 206–208.5°, may be obtained by further recrystallization and a subsequent sublimation at 180–190° (0.5 mm.) (Precision Glass Macro Sublimator No. JM7410), and its use leads to higher yields of α -pyrone (80–85%) by the procedure given here. However, the losses of coumalic acid incurred in the purification (about 50%) and the time involved render this modification unprofitable. On the other hand, when unrecrystallized coumalic acid is used, the yields are generally somewhat lower (60–65%) and the results are slightly more variable.

2. The following apparatus was used by the submitters. The furnace was a Lindberg Model CF-1R High Temperature Combustion Furnace (Fisher Scientific Co. Catalog No. 10-467-1; E. H. Sargent Co. Catalog No. S-35955). This furnace has a hot zone of $8\frac{3}{4}$ in. and a maximum temperature of 1450°C. Because of the short heating length, the Vycor tube was packed with copper turnings over its entire length to prevent condensation of coumalic acid in the cooler parts of the tube. Glass wool insulation was used at both ends of the furnace to prevent heat loss.

The heater used for the sublimation vessel was made from a length of 15-cm. Pyrex tubing. The tube was covered partially with moistened asbestos fiber strips (*ca.* 1 mm. thick) which remain in place when dry. The tube was only partially covered with asbestos to allow visual inspection of the sublimation vessel. A sufficient length of nichrome wire (depending on the resistance of the wire) was wound over the asbestos base, and more asbestos was added over that already in place to hold the wire loops apart. During use, the open end was well stuffed with glass wool.

The sublimation vessel was made from 10-cm. Pyrex tubing sealed at one end and fitted with a standard taper 34/45 female joint at the other end.

The checkers used a Hoskins tube furnace, type FD303A (Central Scientific Co.), 17 in. long. The heater for the sublimation vessel was wound in two sections with heating wire in such a way that a decreasing temperature gradient in the direction of the pyrolysis oven was maintained. The open end of the heater was closed by an asbestos end plate which could be heated independently by a small nichrome coil.

3. Copper appears to function only as a surface heat transfer agent. Broken pieces of porous plate, for example, may also be used.

4. Better yields are obtained at low pressures (preferably below 5 mm.) because of more efficient sublimation of coumalic acid. The submitters report that a water aspirator could be used with crude (unrecrystallized) coumalic acid to avoid damage to the vacuum pump by untrapped corrosive vapors, and that yields of α -pyrone averaged 45% in this modification. The checkers used a mechanical pump with an efficient sodium hydroxide trap in all runs.

5. It is important that the melting of the coumalic acid be prevented during the sublimation process; hence maintenance of the lowest possible pressure is recommended. If the material in the sublimation vessel begins to melt, resinification occurs with no further sublimation and a correspondingly lower yield of product. The temperature of the sublimator should be maintained high enough to allow a maximum rate of sublimation of coumalic acid, but not so high as to cause melting. Increasing the scale of the preparation increases the possibility of resinification of coumalic acid in the sublimator before complete reaction. However, the submitters have successfully carried out the preparation of α -pyrone on twice the scale described here using the same procedure and apparatus (except that the collection flasks were 100-ml. size). On the larger scale it is advisable to use pure sublimed coumalic acid. In the experience of the checkers, larger-scale runs are much less readily reproducible.

3. Methods of Preparation

α -Pyrone has previously been prepared in low yield by the pyrolysis of heavy metal salts of coumalic acid³ and by the small-scale pyrolysis of α -pyrone-6-carboxylic acid over copper.⁴

4. Merits of the Preparation

This method affords α -pyrone in quantity and in good yield not achieved previously.³ The compound has considerable possibilities in Diels-Alder reactions, such as a decarboxylative double diene synthesis.⁵

1 Department of Chemistry, University of Wisconsin, Madison 6, Wisconsin

2. R. Wiley and N. Smith, *Org Syntheses*, Coll Vol 4 201 (1963)

3 H von Pechmann, *Ann*, **264**, 272 (1891)

4. J Fried and R C. Elderfield, *J Org Chem*, **6**, 566 (1941).

5 H E Zimmerman and R. M. Paufler, *J. Am Chem Soc*, **82**, 1514 (1960)

SODIUM NITROMALONALDEHYDE MONOHYDRATE

WARNING

It has been reported (Bruno Camerino, private communication) that, during the preparation of sodium nitromalonaldehyde monohydrate¹ on a pilot-plant scale, two operators were so affected by the fumes evolved during the preparation that their immediate hospitalization was necessary. It was determined subsequently that hydrogen cyanide, up to approximately 1 g./kg. of mucobromic acid utilized, was formed in the reaction mixture. It is essential that precautions specified in Note 1 of the procedure be followed carefully.

1 *Org Syntheses*, Coll Vol. 4, 844 (1963)

PURIFICATION OF TETRAHYDROFURAN

WARNING

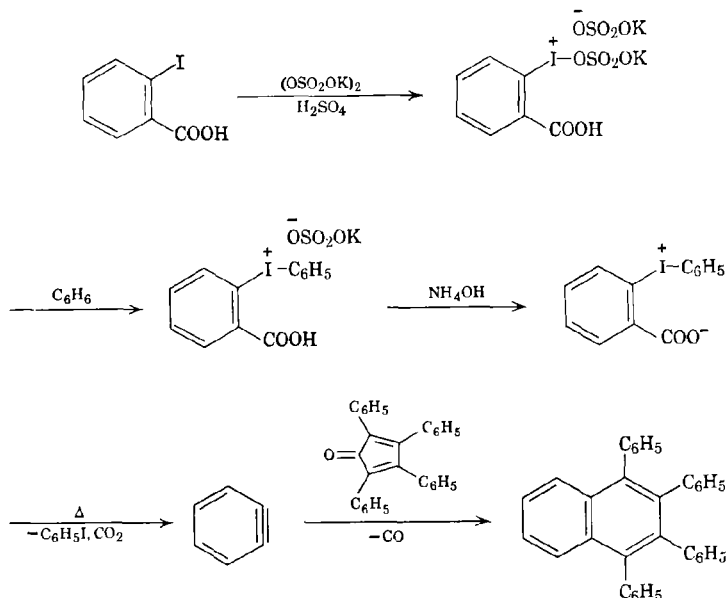
It has been reported that serious explosions may occur when impure tetrahydrofuran is treated with solid potassium hydroxide or with concentrated aqueous potassium hydroxide, as has been recommended widely for the purification of tetrahydrofuran; see *Org. Syntheses*, Coll. Vol. 4, 474, 792 (1963); Vol. 40, 94 (1960). There is evidence that the presence of peroxides in the tetrahydrofuran being purified was causal. It is strongly recommended, therefore, that this method not be used to dry tetrahydrofuran, if the presence of peroxides is indicated by a qualitative or quantitative test with acidic aqueous iodide solution. Traces of peroxide can be removed by treatment with cuprous chloride; see *Org. Syntheses*, 45, 57 (1965). The safety of this operation should be checked first on a small scale (1-5 ml.). It is recommended that tetrahydrofuran containing larger than trace amounts of peroxides be discarded by flushing down a drain with tap water. It must be kept in mind that mixtures of tetrahydrofuran vapor and air are easily ignitable and explosive; purification is best carried out in a hood which is well exhausted and which does not contain an ignition source.

The best procedure for drying tetrahydrofuran appears to be distillation (under nitrogen) from lithium aluminum hydride. This operation should not be attempted until it is ascertained that the tetrahydrofuran is peroxide-free and also not grossly wet. A small-scale test can be carried out in which a small amount of lithium aluminum hydride is added to *ca.* 1 ml. of the tetrahydrofuran to determine whether a larger-scale drying operation with lithium aluminum hydride would be too vigorous for safe operation. Tetrahydrofuran so purified rapidly absorbs both oxygen and moisture from air. If not used immediately, the purified solvent should be kept under nitrogen in a bottle labeled with the date of purification. Storage for more than a

few days is not advised unless 0.025% of 2,6-di-*t*-butyl-4-methyl phenol is added as an antioxidant.

There are no indications that *peroxide-free*, but moisture-containing, tetrahydrofuran cannot safely be predried over potassium hydroxide. However, even this operation should be attempted only after a test-tube scale experiment to make sure that a vigorous reaction does not occur.

A peroxide-free grade of anhydrous tetrahydrofuran (stabilized by 0.025% of 2,6-di-*t*-butyl-4-methyl phenol) is available currently (1966) from Fisher Scientific Co. in 1-lb. bottles. This product as obtained from freshly opened bottles has been found to be suitable for reactions such as the formation of Grignard reagents in which purity of solvent is critical (du Pont Co., unpublished observations). It is standard practice in at least one laboratory to use only tetrahydrofuran (Fisher) from freshly opened bottles and to discard whatever material is not used within 2-3 days.

1,2,3,4-TETRAPHENYLNAPHTHALENE**(Naphthalene, 1,2,3,4-tetraphenyl-)**Submitted by LOUIS F. FIESER and MAKHLUF J. HADDADIN¹

Checked by JOYCE M. DUNSTON and PETER YATES

1. Procedure

A. Diphenyliodonium-2-carboxylate. An Erlenmeyer flask containing 80 ml. of concentrated sulfuric acid (Note 1) is placed in an ice bath to cool. To a 2-l. three-necked flask are added (Note 2) 20 g. (0.081 mole) of lump-free *o*-iodobenzoic acid (Note 3) and 26 g. (0.096 mole) of potassium persulfate (Note 4.) The flask is cooled in an ice bath, the chilled sulfuric acid is added, and the flask is swirled in an ice bath for 4–5 minutes to produce an even suspension and to control the initial exothermal reaction. The flask is then removed from the ice bath and the time is noted.

The reaction mixture foams somewhat and acquires a succession of colors. The flask is mounted in a pan of acetone, a mechanical stirrer with a curved Teflon® blade is placed in the center neck of the flask and operated slowly, and a 250-ml. separatory funnel is mounted into a side neck. Three flasks are put in an ice bath to cool: one containing 190 ml. of distilled water, another 230 ml. of 29% ammonium hydroxide, and another 400 ml. of methylene chloride.

After the oxidation has proceeded for 20 minutes, the acetone bath is brought to 10° by addition of crushed dry ice, and the solution is stirred for 2-3 minutes. There is added 20 ml. of thiophene-free benzene (17.6 g., 0.226 mole), and stirring at 10° is continued for 1 hour (Note 5). The temperature of the acetone bath is lowered to -15° by addition of crushed dry ice and the bath kept at this temperature while the chilled 190 ml. of distilled water is added with efficient stirring to precipitate the potassium bisulfate salt of diphenyliodonium-2-carboxylic acid. The 400 ml. of chilled methylene chloride (Note 6) is added, and a 100° thermometer is mounted in a side neck in such a way that the 15-25° section is visible. With efficient cooling (bath at -15°) and stirring, the 230 ml. of chilled 29% ammonium hydroxide (Note 7) is added at such a rate that the temperature of the reaction mixture remains between 15° and 25°. Approximately 10 minutes is required for the addition, and after the addition the aqueous layer should be alkaline to indicator paper (pH 9). The stirrer and the thermometer are removed and rinsed with water and methylene chloride. The bulk of the aqueous layer is decanted into a 500-ml. Erlenmeyer flask for temporary storage, and the reaction flask is emptied and rinsed into a 500-ml. separatory funnel. The pale tan lower methylene chloride layer is drained into a 1-l. Erlenmeyer flask, the decanted aqueous layer is added to the separatory funnel, and the combined aqueous layer is extracted with two 100-ml. portions of methylene chloride. The combined extract is dried over anhydrous sodium sulfate, filtered into a 1-l. Erlenmeyer flask, and the filtrate is evaporated on the steam bath until the product is left as a dry grayish cake. The cake is dislodged and broken up with a stainless steel spatula, and the bulk of the product is transferred to a

paper. Material adhering to the flask and spatula is dissolved in boiling methylene chloride and the solution transferred to a tared 500-ml. flask and evaporated to dryness. The solid product is added to the flask and the combined solid is brought to constant weight at steam-bath temperature and water-aspirator pressure. The yield of crude product is 23.3–24.4 g. (Note 8).

Boiling water (275 ml.) is poured into the flask, the product brought into solution at the boiling point, and 0.4 g. of Norit® is added carefully to the slightly cooled solution. The solution is again heated to boiling, filtered, and allowed to stand for crystallization overnight, eventually at 0°. The colorless prisms of diphenyliodonium-2-carboxylate monohydrate (Note 9) are collected and air-dried to constant weight at room temperature. The yield of product, m.p. 220–222° (dec.), is 20–22 g. (72–79%, Note 10).

B. *1,2,3,4-Tetraphenylnaphthalene*. To a 100-ml. round-bottomed flask equipped with an 11-cm. water-cooled condenser (Note 11) there is added 60 ml. of diethylbenzene (*meta* and *para* mixture) (Note 12), and the flask is heated in a fume hood with the free flame of a microburner until refluxing liquid rises well into the condenser. If a cloudy zone of condensate appears at the top of the condenser, the moisture is removed with an applicator stick wrapped with absorbent cotton (Note 13). The same technique is used later for removal of water of hydration which appears in the early stages of the reaction and causes hissing and eruption if allowed to drop back into the flask (Note 14). The flame is removed and 10 g. (0.026 mole) of tetraphenylcyclopentadienone² (Note 2) and 11.8 g. (0.035 mole) of diphenyliodonium carboxylate monohydrate are added to the flask. The mixture is heated over a microburner at a rate such as to maintain vigorous gas evolution and gentle refluxing. The water of hydration is eliminated in 8–10 minutes. The flask is then fitted with a normal reflux condenser and the heating is continued. After 30 minutes considerable undissolved diphenyliodonium carboxylate can still be seen, under illumination, at the bottom of the flask. In another 5 minutes the color changes to transparent red, and in a minute or two longer the solution be-

comes pale amber. Refluxing is continued until no solid remains (10–15 minutes) (Note 15). The flask is then fitted for distillation, and 55 ml. of liquid (diethylbenzene and iodobenzene, b.p. 188°) is removed by distillation. The residue is cooled and dissolved in 25 ml. of dioxane. The solution is rinsed into a 125-ml. Erlenmeyer flask and diluted with 25 ml. of 95% ethanol. The solution is heated to boiling, and water (6–7 ml.) is added gradually until a few shiny prisms remain undissolved on boiling. Crystallization is allowed to proceed at room temperature and then for several hours at 0°. The precipitate is removed by filtration, and the mother liquor upon further standing deposits a small second crop of crystals (0.3 g., m.p. 1° low). The main product melts initially in the range 196–199°, solidifies on cooling, and remelts sharply at 203–204° (Note 16). The total yield is 9.2–10.2 g. (82–90%).

2. Notes

1. The amount of acid is half that called for in previous procedures.^{3, 4}

2. The solids are added using a powder funnel or a rolled-up piece of glazed paper to prevent material from lodging on the neck or walls.

3. Obtained from Eastman Organic Chemicals.

4. The fine granular material supplied by Fisher Scientific Co. is satisfactory; any lumps present should be crushed. Persulfate in the form of large prisms should be ground prior to use.

5. If the reactants are mixed at room temperature, a rapid temperature rise of about 7° is noted. The reaction can then be brought to completion by swirling at 50° for 5 minutes or at room temperature for 20 minutes, but the product contains considerable brown pigment.

6. The methylene chloride is added for efficient extraction of the product as it is liberated on neutralization. The product is more soluble in this solvent than in chloroform.^{3, 4}

7. Neutralization with sodium hydroxide^{3, 4} leads to troublesome separation of sodium salts.

8. This crude product contains a little solid which will not redissolve in an organic solvent and it is unsuitable for procedure B. The checkers used a 500-ml. filter flask with sealed side arm for the evaporation and drying operation.

9. *Anal.* Calcd. for $C_{13}H_{11}O_3I$ (342.13): C, 45.63; H, 3.24, I, 37.10. Found: C, 45.48; H, 3.19; I, 37.16.

10. Anhydrous material, m.p. 215–216° (dec.), can be obtained in quantitative yield by extracting 12 g. of the monohydrate in a Soxhlet extractor with 80 ml. of methylene chloride and evaporating to constant weight.

11. A convenient condenser is a water-cooled Ace Glass Bearing, No. 8244.

12. Obtained from Eastman Organic Chemicals, b.p. 175–181°. This solvent, in which the benzyne precursor is very sparingly soluble, seemed slightly superior to trimethylene glycol dimethyl ether (b.p. 222°) in which the solubility is considerably higher. *o*-Dichlorobenzene (b.p. 179°), a still better solvent for the dipolar salt, is less satisfactory than the ether. Diethyl oxalate (b.p. 184°) and *N,N*-dimethylacetamide (b.p. 195°) are unsatisfactory.

13. The checkers found it impossible to prevent water from dropping into the hot mixture and leading to its eruption through the top of the condenser. They found it convenient to eliminate the small condenser and use only a normal condenser where the prolonged reflux period is needed.

14. The yield was not improved by use of anhydrous material (Note 10).

15. Solid adhering to the walls of the flask can be dislodged by loosening the clamp supporting the flask and using the condenser as a lever to swirl the flask.

16. The double melting point has been observed in only one⁵ of the previous studies. The initial melting point varies with the state of subdivision and is not a reliable index of purity. Several recrystallizations did not change the melting behavior or the remelt temperature. The checkers did not observe the double melting point with the product initially obtained, but did so with material recrystallized once.

3. Methods of Preparation

1,2,3,4-Tetraphenylnaphthalene has been isolated by Wittig and co-workers by generation of benzyne in the presence of excess tetraphenylcyclopentadienone as trapping agent. Yields of hydrocarbon isolated by chromatography and based upon the precursor are as follows: from *o*-fluorobromobenzene, 17%;⁶ from either *o*-iodophenylmercuric iodide or bis-(*o*-iodophenyl)-mercury, 25%.⁷ The hydrocarbon has also been obtained in low yield as one of two products resulting from the reaction of diphenylacetylene with triphenylchromium.⁵ The present method is due to Le Goff,⁴ who reports a 68% yield of hydrocarbon from diphenyliodonium-2-carboxylate. However, this investigator states in a private communication that he refluxed the benzyne precursor with a large excess of tetraphenylcyclopentadienone in diethylene glycol dimethyl ether and isolated the hydrocarbon by tedious hexane extraction and chromatography. In the experience of the submitters the solvent selected has too low a boiling point (161°) for efficient conversion.

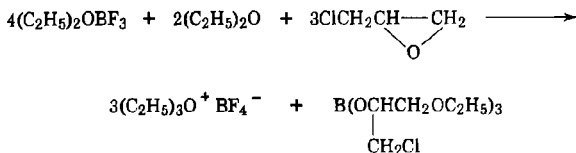
4. Merits of the Preparation

The procedure demonstrates a safe and simple method for the generation of benzyne from a stable and easily prepared precursor and its use in the synthesis of a hitherto difficultly accessible hydrocarbon.

1. Department of Chemistry, Harvard University, Cambridge 38, Massachusetts.
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TRIETHYLOXONIUM FLUOBORATE

(Oxonium compounds, triethyloxonium tetrafluoroborate)

Submitted by H. MEERWEIN¹

Checked by B. C. ANDERSON, O. H. VOGL, and B. C. McKusick

1. Procedure

A 2-l. three-necked flask, a stirrer, a dropping funnel, and a condenser provided with a drying tube are dried in an oven at 110°, assembled while hot, and cooled in a stream of dry nitrogen. Sodium-dried ether (500 ml.) and 284 g. (252 ml., 2.00 moles) of freshly distilled boron fluoride etherate (Notes 1 and 2) are placed in the flask. Epichlorohydrin (140 g., 119 ml., 1.51 moles) is added dropwise to the stirred solution at a rate sufficient to maintain vigorous boiling (about 1 hour is needed). The mixture is refluxed an additional hour and allowed to stand at room temperature overnight. The stirrer is replaced by a filter stick, and the supernatant ether is withdrawn from the crystalline mass of triethyloxonium fluoborate; nitrogen is admitted through a bubbler during this operation to prevent atmospheric moisture from entering the flask. The crystals are washed with three 500-ml. portions of sodium-dried ether. The flask is transferred to a dry box, and triethyloxonium fluoborate is collected on a sintered-glass filter and bottled in a stream of dry nitrogen. The fluoborate is colorless; m.p. 91–92° (dec.), yield 244–272 g. (85–95%) (Note 3).

2. Notes

1. The checkers obtained boron fluoride etherate and epichlorohydrin from Eastman Organic Chemicals and redistilled each through a 23-cm. Vigreux column immediately before use.

2. It is convenient to measure the liquids with syringes using the densities: epichlorohydrin d_4^{25} 1.179; boron fluoride etherate, d_4^{25} 1.125.

3. Triethyloxonium fluoborate is very hygroscopic. It should be stored in a tightly closed screw-cap bottle at 0–5° and should be used within a few days of the time it is made. It should be weighed and transferred in a dry box. It can be stored indefinitely under ether or at –80°.

3. Methods of Preparation

The procedure used is essentially that described by Meerwein and co-workers.^{2, 3} The salt also has been prepared from ethyl fluoride and boron fluoride etherate, and from silver fluoborate, ethyl bromide, and ether.⁴

4. Merits of the Preparation

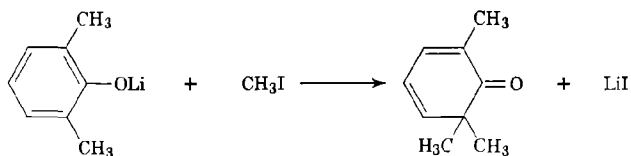
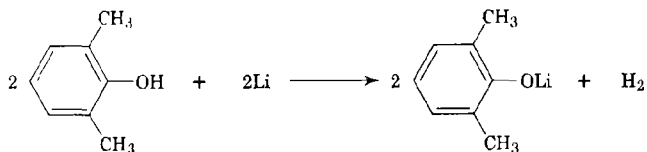
This simple procedure easily provides large amounts of triethyloxonium fluoborate. Triethyloxonium fluoborate readily ethylates such compounds as ethers, sulfides, nitriles, ketones, esters, and amides on oxygen, nitrogen, or sulfur to give onium fluoborates (often isolable) that can react with nucleophilic reagents to give useful products.⁵ For example, dimethylformamide gives the imino ether fluoborate $[(\text{CH}_3)_2\text{NCH—OC}_2\text{H}_5]^+ \text{BF}_4^-$, which is converted to $(\text{CH}_3)_2\text{NCH}(\text{OC}_2\text{H}_5)_2$ by sodium ethoxide.⁵ Since an imino ether fluoborate is easily hydrolyzed to the corresponding amine and ester, triethyloxonium fluoborate is a useful reagent for converting amides to amines under mild conditions.⁸

If there is no advantage in ethylation over methylation, trimethyloxonium fluoborate⁶ or trimethyloxonium 2,4,6-trinitrobenzenesulfonate⁷ may be preferable alkylating agents; their

preparation is more laborious, but they may be stored for a longer period of time.

1. Deceased October 24, 1965; formerly at University of Marburg, Marburg, Germany.
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2,6,6-TRIMETHYL-2,4-CYCLOHEXADIENONE
(2,4-Cyclohexadiene-1-one, 2,6,6-trimethyl-)



Submitted by DAVID Y. CURTIN and ALLAN R. STEIN¹

Checked by WILLIAM G. DAUBEN and JOEL W. ROSENTHAL

1. Procedure

A. Lithium 2,6-dimethylphenoxide. In a 300-ml. flask, equipped with a magnetic stirrer and a reflux condenser and flushed with nitrogen, are placed 150 ml. of toluene (freshly distilled from sodium), 1.40 g. (0.202 mole) of lithium metal (Note 1) and 25.0 g. (0.205 mole) of resublimed 2,6-dimethylphenol. The mixture

is heated under reflux with stirring for 36 hours; a nitrogen atmosphere is maintained for the reflux period (Note 2). The condenser is replaced by a distillation head with a condenser set for distillation, and a distillation capillary is inserted in the thermometer joint. The bulk of the toluene is removed under nitrogen at reduced pressure (Note 3). The distillation head is rapidly removed, and the flask is flushed with nitrogen and closed by a stopper. The stoppered flask is transferred to a dry box flushed with nitrogen, the stopper removed, and the slurry in the flask filtered with suction through a 65-mm. sintered-glass funnel. The collected lithium salt is washed with three 75-ml. portions of hexane (freshly distilled from lithium aluminum hydride), and the white powder (Note 4) is dried at 100–150° and 0.5 mm. pressure to constant weight (3–10 hours is required). The yield of lithium 2,6-dimethylphenoxide as a fine white or light gray powder is 25.0–25.5 g. (98–100%) (Notes 5 and 6).

B. *2,6,6-Trimethyl-2,4-cyclohexadienone*. In a nitrogen-filled dry box, 25.0 g. of lithium 2,6-dimethylphenoxide (0.195 mole) is transferred to an oven-dried, thick-walled Pyrex® bomb tube (650 x 19 mm.). The bomb tube is stoppered with a rubber stopper fitted with a drying tube, removed from the dry box, and 75 ml. of methyl iodide (170 g., 1.20 moles) (freshly distilled from calcium hydride) is quickly pipetted into the bomb under a dry nitrogen stream. The bomb is cooled in a dry-ice bath and sealed with an oxygen torch. After warming to room temperature, the bomb is shaken to disperse the salt cake and placed in a bomb furnace which has been preheated to 135° (Note 7).

After 36 hours the furnace is allowed to cool, the bomb is removed, cooled to dry-ice temperatures, and opened carefully as there may be residual pressure. The golden brown liquid is poured into a 200-ml. flask, and the methyl iodide is removed on a rotary evaporator (*Caution! Hood*). The residue from the flask and the bomb is washed into a 500-ml. separatory funnel with 100 ml. each of ether and 1:1 solution of Claisen's alkali and water (Note 8). The funnel is shaken, and the alkali layer is removed. The ether layer is extracted four additional times with 100 ml. portions of the alkali (Note 9), washed twice with 75-ml. portions of water, once with saturated aqueous salt solution, and

dried by filtration through anhydrous sodium sulfate into a 200-ml. round-bottomed flask. The ether is removed on a rotary evaporator, and the 23.0 g. of yellow oil remaining is allowed to stand at room temperature for 7–10 days to permit dimerization of the dienone (Note 10).

The 2,6-dimethylanisole is removed by vacuum distillation (nitrogen capillary bubbler) at 35–50° (0.75 mm. or less pressure). The solid dimerized product² in the residue is either recrystallized twice from the minimum amount of hot hexane or vacuum-distilled, b.p. 175° (25 mm.) (Note 11) followed by a single recrystallization from hexane.

The yield of purified 2,6,6-trimethyl-2,4-cyclohexadienone dimer (white needles, m.p. 119.5–121.0°) is 4.8–5.1 g. (18–19%) (Note 12), and the yield of 2,6-dimethyl anisole is 13.5–14.0 g. (51–53%).

The dienone monomer may be regenerated from its dimer as desired by heating the dimer above 170° for several minutes in a test tube and quenching, or by distillation at 25 mm. (Note 11) through a short condenser into a dry ice-acetone cooled receiver. The monomer may be stored for several days at dry-ice temperatures without appreciable dimerization.

2. Notes

1. The lithium should be added in the form of very small pieces. The pieces are most conveniently prepared as follows. Trim the oxide layer off a small block of lithium metal under mineral oil, grip it with tweezers and rinse the mineral oil off in a beaker of dry ether. Hold the block in the ether vapors momentarily to dry, and then plunge it into a tared beaker of mineral oil for weighing. Cut the block into strips with a sharp knife, remove the pieces one by one, and squeeze them into long flat ribbons with pliers which are frequently dipped into the mineral oil. Cut the ribbons into short sections over another beaker of dry ether, swirl and transfer the pieces to a third beaker of ether to wash off the last traces of mineral oil before adding the lithium to the reaction flask.

2. A positive pressure of nitrogen is maintained by attachment of a mercury bubbler on the top of the reflux condenser.

3. If heating is desired to speed the toluene removal, a steam or an oil bath is used to prevent charring of the salt.

4. If the salt is lumpy, it is best to grind it into a fine powder in an agate mortar before washing it with the hexane. The fine powder is more easily washed and reacts more readily in the alkylation reaction.

5. The lithium phenoxide may be prepared in larger quantities and may be stored for some time sealed under nitrogen and protected from light by wrapping the flask with aluminum foil. Traces of water lead to a gummy salt, while traces of oxygen cause a purple coloration. Quite badly discolored salt has been used successfully in the alkylation procedure, but yields tend to be reduced by tar formation.

6. Titration of a portion of the salt with 0.1*N* hydrochloric acid to methyl orange end-point shows the salt to be 97–103% lithium 2,6-dimethylphenoxide.

7. The temperature used is not crucial, but the best yield is obtained in the 120–180° range. At higher temperatures considerable tar forms, while at lower temperatures dienone yields are sacrificed.³

8. Claisen's alkali is a solution of 350 g. of potassium hydroxide in 250 ml. of water made up to 1 liter with methanol.

9. About 4.5 g. or 18% of the starting 2,6-dimethylphenol may be recovered from the combined alkaline extracts by acidification with concentrated hydrochloric acid and extraction of the liberated phenol with ether.

10. The Diels-Alder dimerization of 2,6,6-trimethyl-2,4-cyclohexadienone to 1,4,6,6,9,9-hexamethyl- $\Delta^{3,11}$ -tricyclo-[6.2.2.0^{2,7}]-dodecane-5,10-dione² facilitates its separation from the major alkylation product, 2,6-dimethylanisole.

11. In the distillation of the dienone it is necessary to maintain a pot temperature of 175–200° to reverse the dimerization (Note 10).

12. An additional 0.5–1.0 g. of the dienone dimer may be obtained by allowing the 2,6-dimethylanisole fraction to stand for several days and then redistilling it.

3. Methods of Preparation

This preparation of 2,6,6-trimethyl-2,4-cyclohexadienone is based upon the published procedure of the submitters,² and it is the only preparation of the 2-substituted-2,4-cyclohexadienones. The simpler 6,6-dimethyl-2,4-cyclohexadienone is more conveniently prepared by the method of Alder.⁴

4. Merits of the Preparation

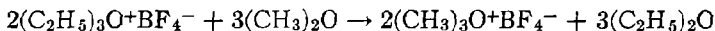
The use of lithium in toluene for the preparation of alkali metal phenoxides appears to be the most convenient and least expensive procedure. The procedure also has the merit of giving the salt as a finely divided powder.

The alkylation procedure can be used to prepare a wide variety of 2-substituted-2,4-cyclohexadienones,^{2, 3, 5, 6} which are useful starting materials. The compounds can serve either as dienes or dienophiles⁷ in the Diels-Alder reaction and can be opened photochemically to yield substituted $\Delta^{3,5}$ -hexadienoic acids.⁸

1. Department of Chemistry and Chemical Engineering, University of Illinois, Urbana, Illinois.
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TRIMETHYLOXONIUM FLUOBORATE

(Oxonium compounds, trimethyloxonium tetrafluoroborate)



Submitted by H. MEERWEIN¹

Checked by O. VOGL, B. C. ANDERSON, and B. C. MCKUSICK

1. Procedure

Freshly prepared triethyloxonium fluoborate² (170 g., 0.90 mole) is dissolved in 500 ml. of anhydrous methylene chloride in a 1-l. three-necked flask equipped with a stirrer, gas-inlet tube, and drying tube (Note 1). The reaction flask is immersed in an ice bath, the stirrer is started, and 138 g. (3.00 moles) of dry dimethyl ether is passed into the solution from a tared cylinder over a period of about 2 hours. The reaction mixture is allowed to stand overnight at room temperature. An hour after the addition of dimethyl ether is complete, trimethyloxonium fluoborate begins to separate. The initially liquid product solidifies slowly.

The stirrer is replaced by a filter stick, and the supernatant methylene chloride is withdrawn from the crystalline mass of trimethyloxonium fluoborate, nitrogen is admitted through a bubbler during this operation to prevent atmospheric moisture from entering the flask. The crystals are washed with three 100-ml. portions of anhydrous methylene chloride. The flask is transferred to a dry box, and trimethyloxonium fluoborate is collected on a sintered-glass filter, dried for 2 hours in a vacuum desiccator at 25° (1 mm.), and bottled in a stream of dry nitrogen. The fluoborate is colorless; m.p. 141–143° with darkening and slight decomposition, yield 114–124 g. (86–94%).

2. Notes

1. In order to obtain maximum yields, all operations must be carried out under rigorously dry conditions. The apparatus

should be dried in an oven at 110°, assembled while hot, and cooled in a stream of dry nitrogen. The checkers dried the methylene chloride over PA 100 silica gel (12–28 mesh) obtained from Davison Chemical Co., Baltimore, Maryland.

2. Trimethyloxonium fluoborate is less hygroscopic and keeps better than triethyloxonium fluoborate, but it should be stored at 0–5° in a tightly closed screw-cap bottle.² So stored, it can be kept at least a few weeks.

3. Methods of Preparation

The procedure used is essentially that described by Meerwein and co-workers.³ The salt has also been prepared from the same reagents in a sealed tube.⁴

4. Merits of the Preparation

This facile preparation is suitable for preparation of larger amounts of salt. Like triethyloxonium fluoborate,² trimethyloxonium fluoborate is a potent alkylating agent. In comparison with trimethyloxonium 2,4,6-trinitrobenzenesulfonate,⁵ trimethyloxonium fluoborate is easier to make but does not keep quite as well on storage.

1 Deceased October 24, 1965, formerly at University of Marburg, Marburg, Germany

2 H. Meerwein, *Org. Syntheses*, this volume, p. 113

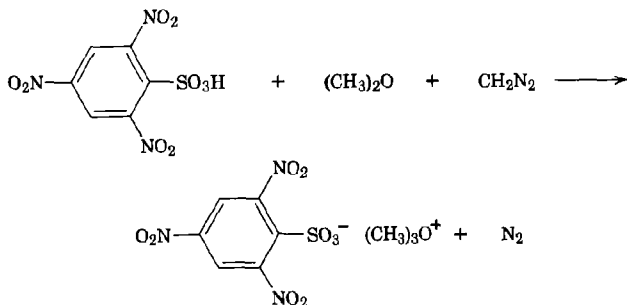
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5 G. K. Helmkamp and D. J. Pettitt, *Org. Syntheses*, this volume, p. 122

**TRIMETHYLOXONIUM 2,4,6-
TRINITROBENZENESULFONATE**

(Oxonium compounds, trimethyloxonium 2,4,6-
trinitrobenzenesulfonate)



Submitted by G. K. HELMKAMP and D. J. PETTITT¹

Checked by O. VOGL, B. C. ANDERSON, and B. C. MCKUSICK

1. Procedure

Caution! Diazomethane is hazardous. Follow the directions for safe handling of diazomethane given in earlier volumes.^{2, 3} All operations are carried out in a hood.

The apparatus is shown in Fig. 2. Two 500-ml. round-bottomed flasks *without standard-taper joints* (which could cause diazomethane to detonate) are used. The gas inlet *C* is connected to a cylinder of dimethyl ether. Gas inlet *C* is long enough to reach near the bottom of flask *A*, but tubing *D* extends only about half-way into flask *B*. A calcium chloride drying tube is attached to the gas outlet *E*. Flask *B* contains a Teflon[®]-covered stirring bar. The pieces of the apparatus are dried in an oven at 110°; well-dried apparatus is essential for a good yield.

A solution of diazomethane in 200 ml. of xylene is prepared from 15.0 g. (0.146 mole) of nitrosomethylurea⁴ (Note 1). The diazomethane solution is decanted into flask *A*, and about 20 g. of

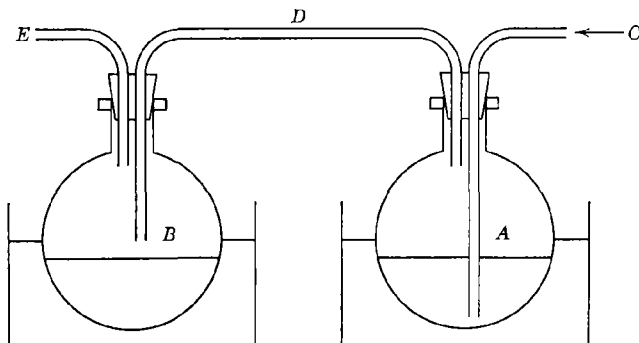


FIG. 2.

potassium hydroxide pellets is added to the solution. The mixture is swirled for a few seconds to ensure removal of most of the water. About 4.2 g. (0.10 mole) of diazomethane is present. Flask *A* is then immersed in a water bath at 20–25°.

2,4,6-Trinitrobenzenesulfonic acid (14.7 g., 0.050 mole) (Note 2), previously dried for at least 1 hour at 80–100° (1 mm.), is placed in flask *B*, which is then immersed to the level shown in Fig. 2 in a bath of acetone maintained at –35° to –40° by addition of small amounts of dry ice (Note 3). About 200 ml. of dimethyl ether is rapidly poured from an ampoule into flask *B* (Note 3). Flasks *A* and *B* are connected as shown in Fig. 2, and magnetic stirring is started in flask *B*. When most of the sulfonic acid has dissolved, gaseous dimethyl ether is introduced through *C* at such a rate that a rapid stream of individual bubbles passes through the diazomethane solution in flask *A*. In the course of the reaction all the acid goes into solution and is replaced by a fluffy precipitate of the oxonium salt. The introduction of dimethyl ether is discontinued as soon as the supernatant solution in flask *B* turns yellow (Notes 5 and 6).

Flask *B* is separated from the apparatus but kept in the cooling bath, and 200 ml. of anhydrous ethyl acetate is added; addition is slow so as to avoid excessive boiling of the dimethyl ether (Note 7). The flask, with a tube of calcium chloride attached, is gradually brought to room temperature; most of the dimethyl

ether evaporates during this operation. Crystalline trimethyloxonium 2,4,6-trinitrobenzenesulfonate is separated on a coarse sintered-glass funnel, washed with two 25-ml. portions of ethyl acetate and with 50 ml. of high-boiling petroleum ether, and dried over phosphorus pentoxide at 25° (<1 mm.) (Note 8); yield 12–14 g. (68–79%) (Note 9), m.p. 181–183° (Note 10).

2. Notes

1. Xylene is used as the solvent instead of diethyl ether because of its considerably lower vapor pressure.

2. 2,4,6-Trinitrobenzenesulfonic acid from Nutritional Biochemical Corp., Cleveland, Ohio, can be used without any purification other than drying. The checkers observed m.p. 174–177° for the dried acid.

The acid can be prepared from picryl chloride according to the method described by Golumbic, Fruton, and Bergmann,⁵ but the following modifications are recommended: sodium metabisulfite should be used in place of sodium bisulfite; the crude sodium salt is not recrystallized but is converted directly to the acid by the addition of hydrochloric acid to its acetone solution; the product is recrystallized by dissolving it in a minimum amount of hot acetone, adding chloroform until crystallization starts, and cooling to about 0°. Two recrystallizations yield a product with m.p. 194–196°.

3. If the level of the cooling bath is too high, or if the bath temperature is less than –40°, unnecessary condensation of dimethyl ether occurs. If the level of the bath is too low, a brownish ring of decomposition product forms in the flask. Since the brown material is soluble in dimethyl ether and ethyl acetate, it does not contaminate the trimethyloxonium salt.

4. The submitters first transferred the dimethyl ether from a cylinder to an ampoule in order to avoid the accumulation of excess water. The ampoule should have a moderately wide mouth in order to facilitate rapid transfer of dimethyl ether.

The checkers made a mark on flask *B* corresponding to a volume of 220 ml., added the acid and stirrer, immersed the flask

in liquid nitrogen, and passed in gaseous dimethyl ether from a cylinder until the volume of condensate reached the mark.

5. Diazomethane reacts with 2,4,6-trinitrobenzenesulfonic acid with ring opening similar to that observed with 1,3,5-trinitrobenzene.⁶ Hence an excess of the reagent is to be avoided. The yellow color is not due to the presence of diazomethane itself. The reaction time is highly sensitive to the temperature of the xylene solution and to the flow rate of gaseous dimethyl ether. The reaction time is usually 20–40 minutes.

6. The excess diazomethane in flask A should be destroyed by adding a few drops of glacial acetic acid.

7. The ethyl acetate acts only as a high-boiling material that makes the subsequent vacuum filtration easier to control.

8. If the product is air-dried for more than a few seconds on the filter, it may pick up a significant amount of water. Most of the solvent that remains with the crystals should be removed under vacuum.

9. The product at this stage of purification is sufficiently pure for synthetic applications. As measured by the amount of dimethyl ether evolved on heating, its purity is about 95%.

10. On very rapid heating, the compound effervesces at about 120–130°. It then resolidifies and melts again at 181–183°, which is the melting point of methyl 2,4,6-trinitrobenzenesulfonate. At low heating rates, the effervescence may not be noticed.

3. Methods of Preparation

This method for the preparation of trimethyloxonium 2,4,6-trinitrobenzenesulfonate is an adaptation of that described by the submitters.⁷ The salt can also be prepared from trimethyloxonium fluoborate by anion exchange.⁷ Trimethyloxonium fluoborate⁸ and hexachloroantimonate^{9–11} have been prepared by other methods.

4. Merits of the Preparation

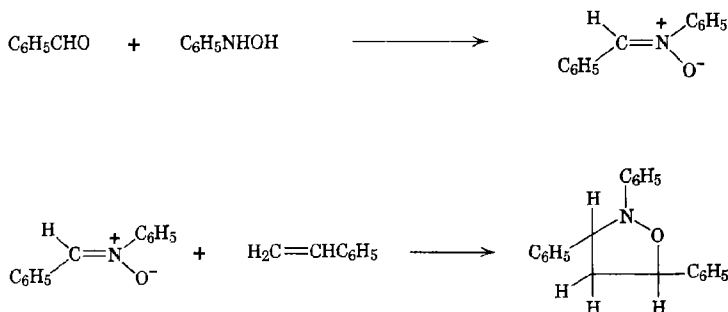
Like triethyloxonium fluoborate,¹² trimethyloxonium 2,4,6-trinitrobenzenesulfonate is a potent alkylating agent. Tri-

methyloxonium 2,4,6-trinitrobenzenesulfonate is nonhygroscopic and hence keeps better than trimethyloxonium fluoborate,⁸ but it is more laborious to make.

- 1 (a) Department of Chemistry, University of California, Riverside, California
(b) Pioneering Research Laboratory, Textile Fibers Department, Experimental Station, E I du Pont de Nemours & Co., Inc., Wilmington 98, Delaware
This work was supported in part by grant AM-08185 of the National Institutes of Health, U S Public Health Service
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2,3,5-TRIPHENYLISOXAZOLIDINE

(Isoxazolidine, 2,3,5-triphenyl-)



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1. Procedure

A. *N*, α -Diphenylnitrone. A solution of 27.3 g. (0.25 mole) of pure *N*-phenylhydroxylamine² (Note 1) in 50 ml. of ethanol is prepared in a 200-ml. Erlenmeyer flask by swirling a mixture of the two and warming it briefly to 40–60° (Note 2). To the clear, lightly colored solution is added 26.5 g. (25.3 ml., 0.25 mole) of freshly distilled benzaldehyde (exothermic reaction). The flask is stoppered and kept overnight at room temperature in the dark. The colorless needles of *N*, α -diphenylnitrone are collected on a Büchner funnel and washed once with 20 ml. of ethanol. There is obtained 42–43 g. (85–87%) of product (m.p. 111–113°), which can be further purified by dissolving the crude material in 80 ml. of ethanol and allowing the solution to cool for several hours in the ice box. In this manner there is produced 35–39 g. (71–79%) of pure crystalline nitrone, m.p. 113–114° (Note 3).

B. 2,3,5-Triphenylisoxazolidine. In a 100-ml. two-necked flask

provided with a reflux condenser and a gas-inlet tube are placed 20.0 g. (0.101 mole) of pure *N*, α -diphenylnitrone and 50 ml. (0.43 mole) of freshly distilled styrene (Note 4). The flask is heated at 60° for 40 hours under a slow nitrogen stream. The mixture is then cooled, and most of the excess styrene is removed (Note 5) from the clear orange solution by heating at a bath temperature of 55° (12 mm.). The warm residue is poured into 40 ml. of petroleum ether (40–60°), whereupon the isoxazolidine crystallizes immediately (Note 6). The flask is rinsed twice with 20-ml. portions of petroleum ether, and the washings are combined with the product. The resulting mixture is cooled for 1 hour in the ice box, and the lightly colored crystals are collected on a Büchner funnel and washed with two 20-ml. portions of petroleum ether. The yield of crude air-dried isoxazolidine (m.p. 96–98°) is 28–30 g. (92–99%).

For further purification the product is dissolved in 40 ml. of methylene chloride in a 250-ml. Erlenmeyer flask. The solution is heated to boiling, and 30 ml. of methanol is added (Note 7). When the solution has cooled to room temperature, 70 ml. of methanol is added to complete the crystallization, and the solution is kept in the ice box for 3 hours. The colorless needles are collected by vacuum filtration and washed with two 30-ml. portions of cold methanol. There is obtained 23–25 g. (76–82%) of product which melts at 99–100° (Notes 8–10).

2. Notes

1. The *N*-phenylhydroxylamine should be free of sodium chloride. This is easily attained by dissolution of the compound in benzene followed by filtration and then addition of petroleum ether to cause rapid crystallization.

2. On prolonged heating, *N*-phenylhydroxylamine begins to decompose.

3. The compound is light-sensitive and should be kept in a brown container.

4. The styrene should be redistilled and stabilized with 0.1% hydroquinone just prior to use; otherwise the final product will

be contaminated with polystyrene. The checkers used approximately 60 ml. (0.52 mole) of styrene.

5. The checkers found that, if all the styrene is removed, the product may become too viscous to pour.

6. By this method the formation of a thick crustaceous material, which is difficult to pulverize or wash, is avoided.

7. In this way the boiling solution is kept clear.

8. From the mother liquor a second diastereoisomer can be isolated (m.p. 78.5–79.5°) in about 10% yield by fractional crystallization.

9. In an analogous manner several other isoxazolidines can be prepared. From the reaction of *N*, α -diphenylnitrone with 1,1-diphenylethylene, 2,3,5,5-tetraphenyliisoxazolidine is obtained. As above, 10.0 g. (50.7 mmoles) of diphenylnitrone is heated under a nitrogen atmosphere for 24 hours at 85° with 15.3 g. (15.0 ml., 85.0 mmole) of 1,1-diphenylethylene.³ The excess olefin is removed at 105–130° (bath temperature) under high vacuum (0.005 mm.). The yellow-gold viscous residue is dissolved by warming it in a mixture of 15 ml. of methylene chloride and 30 ml. of methanol; on cooling, crystallization commences. After 2 hours another 10 ml. of methanol is added, and the mixture is cooled overnight in the ice box. The colorless crystals are collected on a Büchner funnel and washed twice with 20-ml. portions of methanol. The yield of air-dried product (m.p. 113–115°) is 14–16 g. (73–84%). The compound can be further purified by adding methanol (30 ml.) to a boiling solution in methylene chloride (15 ml.). After the solution has cooled to room temperature, another 10 ml. of methanol is added; the mixture is kept in the ice box for several hours and then filtered. The pure compound melts at 115–116°, yield 13–15 g. (68–79%).

10. The preparation of the oily ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate provides another example of this reaction. As in the procedure described with styrene, 10.0 g. (50.7 mmoles) of *N*, α -diphenylnitrone is heated under nitrogen for 24 hours at 90–100° with 35.0 g. (38.0 ml., 307 mmoles) of ethyl crotonate. The excess olefin, b.p. 45° (12 mm.) is removed on the water pump, and the red-orange residue, while still warm, is transferred to a 50-ml. Claisen flask using acetone as a rinse.

After removal of the solvent, 13–14 g. (82–88%) of the isoxazolidine is obtained as an orange oil by high-vacuum distillation at 163–173° (0.003 mm). Redistillation of this material yields 2–3 g. of fore-run and a purer product obtained as a yellow oil, b p 165–170° (0.003 mm), n_D^{20} 1.5602–1.5612.

3. Methods of Preparation

N, α -Diphenylnitrone was first obtained by Bamberger⁴ from N-phenylhydroxylamine and benzaldehyde. The procedure described above is analogous to that of Wheeler and Gore.⁵

2,3,5-Triphenylisoxazolidine, 2,3,5,5-tetraphenylisoxazolidine, and ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate have been prepared only by this method.⁶

4. Merits of the Preparation

The procedure described illustrates the use of 1,3-dipolar addition⁷ of nitrones to olefins for the preparation of isoxazolidines. The preparations of 2,3,5,5-tetraphenylisoxazolidine and ethyl 2,3-diphenyl-5-methylisoxazolidine-4-carboxylate, as described in Notes 9 and 10, respectively, indicate the versatility of the method.

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SUBJECT INDEX

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Names in small capital letters refer to the titles of individual preparations. A number in ordinary boldface type denotes the volume. A page number in boldface italics indicates that the detailed preparative directions are given or referred to, entries so treated include principal products and major by products, special reagents or intermediates (which may or may not be isolated) compounds mentioned in the text or Notes as having been prepared by the method given and apparatus described in detail or illustrated by a figure. Page numbers in ordinary type indicate pages on which a compound or subject is mentioned in connection with other preparations.

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NOMENCLATURE

Preparations appear in the alphabetical order of common names of the compounds. For convenience in surveying the literature concerning any preparation through *Chemical Abstracts* subject indexes, the *Chemical Abstracts* indexing name for each compound is given as a subtitle if it differs from the common name used as the title.

SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds which are of general interest, as well as procedures which illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should have been checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the **range** of yields should be reported rather than the maximum yield obtainable by an operator who has had considerable experience with the preparation. For each solid product the melting-point **range** should be reported, and for each liquid product the **range** of boiling point and refractive index should be included. In some instances, it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, or nuclear magnetic resonance spectra. The methods of preparation or sources of the reactants should be described in notes, and the physical properties (such as boiling point, index of refraction, melting point) of the reactants should be included except where rather standard commercial grades are specified.

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the current style sheet may be obtained from the Secretary of the Editorial Board. In Section 3, **Methods of Preparation**, there should be described other practical methods for preparing the compound which have appeared in the literature. It is unnecessary to mention methods which have been published but are of no practical synthetic value. In Section 4, **Merits of the Preparation**, a statement should be made indicating why the preparation is published in *Organic Syntheses*. Among the obvious reasons for publication would be the novelty of the procedure, general scope of the synthetic method, specific interest in the compound or its use as an intermediate for preparing other compounds, convenience of the method, and improvement in yields. Three copies of each procedure should be submitted to the Secretary of the Editorial Board. It is sometimes helpful to the Board if there is an accompanying letter setting forth the features of the preparation which are of interest.

Additions, corrections, and improvements to the preparations previously published are welcomed and should be directed to the Secretary.

EDITOR'S PREFACE

One aim of the series *Organic Syntheses*, like its format, has held essentially constant for nearly half a century despite the revolutionary events in organic chemistry during that period: the effort to narrow the formidable gap between the *possible* and the *readily attainable* in synthesis through the careful selection, checking, and publication of detailed experimental procedures. The rapid development and growing complexity of new synthetic methodology at all levels have functioned to maintain the value of this approach to the student, to the specialist in synthesis, and by no means least, to the chemist whose primary concern lies in areas other than synthesis. At the same time, these massive advances have generated new responsibilities which have led to new policies and new commitments for this series over the past decade. Summaries of these evolutionary changes appear in the prefaces to Volumes 41 through 45. The recent trends are sustained in Volume 46, in which emphasis has been placed on procedures which illustrate new or neglected *general* methods of synthesis, procedures for the preparation of valuable reagents, procedures for the generation and interception of unstable reaction intermediates, and procedures for the direct and efficient synthesis of novel or fundamental structural types.

On the pages which follow, general methods are illustrated for the synthesis of a wide variety of classes of organic compounds including *acyl isocyanates* (from amides and oxalyl chloride; p. 16), *epoxides* (from reductive coupling of aromatic aldehydes by hexamethylphosphorous triamide; p. 31), α -*fluoro acids* (from 1-alkenes; p. 37), β -*lactams* (from olefins and chlorosulfonyl isocyanate; p. 51), *1,3,5-triketones* (from dianions of 1,3-diketones and esters; p. 57), *sulfinate esters* (from disulfides, alcohols, and lead tetraacetate; p. 62), *carboxylic acids* (from carbonylation of alcohols or olefins via carbonium-ion intermediates; p. 72), *sulfoxides* (from sulfides and sodium periodate; p. 78), *carbazoles*

(from aromatic azides via nitrene intermediates; p. 85), and *isoxazolidines* (from 1,3-dipolar cycloaddition of nitrones to ethylenic systems; pp. 96, 127). Three diverse synthetic routes to *aldehydes* are exemplified: electrophilic arylation of formaldoxime by diazonium salts (p. 13), the Arnold method from ketones and the Vilsmeier reagent (p. 18), and the Krohnke method via nitrones (p. 81).

Among the important reagents for which preparative procedures are given are: 2,2'-bipyridine (by nickel directed and catalyzed dehydrogenation of pyridine; p. 5), formamidine acetate (p. 39), phenyltrichloromethylmercury (p. 98), and trimethyl- and triethyloxonium fluoroborate (pp. 120, 113). The preparation of palladium catalyst ("Lindlar") for the selective reduction of acetylenes is described (p. 89), as is the use of diphenyliodonium-2-carboxylate, as a precursor of benzyne in the synthesis of 1,2,3,4-tetraphenylnaphthalene (p. 107).

In addition, directions are given in Volume 46 for the synthesis of 3,4-dichloro-1,2,3,4-tetramethylcyclobutene (p. 34), 10-methyl-10,9-borazarophenanthrene (p. 65), perchlorofulvalene (p. 93), and α -pyrone (p. 101), molecules which by any standard deserve the designation unique.

The Editorial Board is keenly aware that the success of this enterprise depends heavily on its relevance to current developments and needs in chemistry. Therefore we welcome the assistance of the reader in the form of submissions for publication or suggestions for future volumes while expressing our thanks to the many who have contributed in the past.

Finally, it falls to this Editor to record with sadness the passing of Dr. Oliver Kamm, one of the founders of *Organic Syntheses*, and of Dr. Arthur C. Cope, an outstanding board member for many years.

E. J. COREY

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